RAD
Croatian Academy of Sciences and Arts - Medical Sciences

Editorial Board
Uredništvo

Vol 556 = 62-63 (2023)
knjiga 556, svezak 62-63

doi 10.21857/y6zolb3l1m
ISSN 1848-641x (online)
ISSN: 1330-5301 (print)

Publisher
Izdavač
Croatian Academy of Sciences and Arts
Department of Medical Sciences
Hrvatska akademija znanosti i umjetnosti
Razred za medicinske znanosti

For the Publisher
Za izdavača
Dario Vretenar

Web Editor / Web urednik
Filip Đerke

Graphic designer / Grafička urednica
Nina Ivanović

Edition / Naklada
200

DOI numbers / DOI brojevi
Kristina Polak Bobić

Redaction address:
Trg Nikole Šubića Zrinskog 11, Zagreb
tihana@hazu.hr

RAD CASA was founded by the Croatian Academy of Sciences and Arts in 1867, the Journal: **RAD CASA - Medical Sciences** was founded by the Academy's Department of Medical Sciences in 1951.

The articles are categorized according to "Guidelines for Authors" available at the RAD CASA Medical Sciences webpage: **www.rad-med.com**

RAD CASA Medical Sciences is published twice a year as a double issue.

RAD CASA Medical Sciences is included in / indexed by:

Printed with support of the Foundation of the Croatian Academy of Sciences and Arts

Editorial Policies and Guidelines for Authors

RAD CASA - Medical Sciences is an international peer-reviewed medical journal open to physicians and scientists from the field of biomedicine. It accepts contributions in the form of original article, review, short review, case report, letter to the editor, short communication, and correspondence.

Plagiarism detection

Manuscripts are checked for text similarity and manually verified by the research integrity editor. We use CrossRef Similarity Check software and deal with manuscripts suspected on plagiarism following the COPE flowcharts and ICMJE guidelines.

Ethical approval and informed consent

When reporting trials on human subjects, authors should indicate whether the procedures were following the ethical standards set by the responsible human experimentation committee (institutional and national) and the latest version of the Declaration of Helsinki given by World Medical Association. Ethical approval (institutional or national) should be obtained for every study that includes the collection of an additional patient sample of any biological material (more than those required for the medical evaluation). Regardless of the preserved anonymity, patients presented in case report articles should always sign informed consent. Case reports without patients' consent are not eligible for publication in Rad.

Language

Rad is published exclusively in English. It is the author's responsibility to ensure that the English language is thoroughly revised before submitting the work for publication. Note that the Editorial Board reserves the right to reject a manuscript if the use of language is deemed too poor. The Abstract should be written in both English and Croatian if it is possible (if not, the proofreader will translate it to Croatian).

Article-Processing charges

Manuscript submission, article processing and publishing are free of charge.

Article types

Contributions to the Journal are classified into the categories listed in the table below. The maximum word count does NOT include the title, authors and affiliations, abstract, keywords, subheadings, table and figure legends, and references. However, it does include the text in the tables, if any.

Type	Max. word count	Max. number of refernces
Letter to the editor	1000	5
Review	5000	100
Short review	3500	50
Original article	5000	30
Short communication	1500	10
Case report	1500	20
Correspondence	1000	7

Authorship

Rad follows the guidelines for authorship set forth by the International Committee of Medical Journal Editors (ICMJE)

Each author should meet all four criteria as follows:

1. substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data
2. drafting the article or revising it critically for important intellectual content
3. final approval of the version to be published
4. agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

According to ICMJE: "In addition to being accountable for the parts of the work the author has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. Also, the authors should have confidence in the integrity of the contributions of their co-authors. All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors."

Rad adopted the system by which each author is identified with his/her unique identification number, ORCID, thus ensuring transparency in authorship and personal identification. It is available for free at http://orcid.org/. It is recommended for each author to provide his/her ORCID number.

Manuscript submission

During the manuscript, submission process corresponding author is asked to provide his ORCID ID number. The corresponding author is responsible to fill in the Submission form on behalf of all co-authors. Manuscript Submission form consists of the following sections: authorship statement, statement of originality, conflict of interest disclosure, protection of research participants, and copyright transfer and publication license.

Instructions for authors comply with the "Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly work in Medical Journals" (http://www.icmje.org/recommendations/, updated in 2016). Editors hold the right to make all the necessary changes to the language and style of the original manuscript to adhere to the uniform standards of the Journal.

Manuscript preparation

The manuscript should be written in English and uploaded via the online submission system available at Journal website (**www.rad-med.com**)

The following should be submitted:

- Cover letter
- Title page
- Manuscript (without authors and affiliations)
- Figure (optional)
- Supplementary material (optional).

Please note that a Manuscript file should not contain any information on the authors and their affiliation. Also, the Manuscript file name should not contain any reference to the author's name. This is important because all manuscripts are sent for blind peer review.

All pages of the manuscript (except for the cover letter and title page, which are attached separately) should be within a single document. Original manuscripts should be structured as follows: Abstract, Keywords, Introduction, Materials and Methods, Results, Discussion, Acknowledgments, Tables and Figures, and References.

Abstract All types of manuscripts should contain an abstract. An abstract of 350 words maximum should be provided on a separate page in the Manuscript file (abstract only, without authors and affiliation). The abstract of an original article should be structured into four headings: Introduction, Materials and Methods, Results, and Conclusions. For other article types, abstracts do not have to be structured.

Keywords Please whenever possible, provide 3-5 keywords from MeSH database)

Introduction In the Introduction section, the authors should point out new information in the manuscript, the hypothesis, and the aim of their work. The Introduction section should not contain results and conclusions.

Materials and methods The Materials and methods section should only include information that was available at the time the study was planned. All information obtained during the study should be provided in the Result section. The detailed instructions for writing materials and methods are available at the Journal website (**www.rad-med.com**).

Results State the main or most important finding first. The data presented in the tables or figures should not be repeated in the text. Graphs should be used as an alternative to tables with many entries.

Discussion Emphasize the new and important conclusion based on the study results in the context of the best available evidence. Do not repeat the data presented in the Introduction or Results section. Clearly, state the limitations of the study.

Acknowledgements All contributors who do not meet the authorship criteria should be listed in the Acknowledgments section. These persons must give verbal permission to be acknowledged. Authors should provide that statement during the manuscript submission process. Financial and material support should also be acknowledged and reported in the conflict of interest disclosure during the manuscript submission process.

References Authors are responsible for verifying the accuracy of the references by using an electronic bibliographic source, such as PubMed, or printed original articles. References must not refer to the retracted article except if the authors want to refer to the particular retraction.

Rad applies the Vancouver referencing style. Literature citation should conform to the standards available at NLM's International Committee of Medical Journal Editors (ICMJE) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals (examples are available at Journal website (**www.rad-med.com**)

References should be numbered consecutively, using Arabic numerals in parentheses, in the order of appearance in the text.

Conflict of interest

According to the International Committee of Medical Journal Editors (ICMJE): "Conflict of interest exists when an author (or the author's institution) has financial (employment, consultancies, stock ownership, honoraria and paid expert testimony) or personal relationship, academic competition or intellectual passion that inappropriately influences his actions."

Other possible conflicts of interest

All reviewers, editors, section editors, Editorial Board members, included in the publication process will also be asked to disclose any potential conflict of interest regarding the manuscript they are asked to review (primarily relationships with the pharmaceutical industry; incorporated into our submission system).

For more detailed information and instructions for authors, we suggest visiting the Journals' official webpage: **www.rad-med.com**

RAD
Croatian Academy of Sciences and Arts - Medical Sciences

Vol 556 = 62-63 (2023)
knjiga 556, svezak 62-63

Contents

RAD
HRVATSKE AKADEMIJE ZNANOSTI I UMJETNOSTI
MEDICINSKE ZNANOSTI

VOL 556 = 62-63 (2023)
KNJIGA 556, SVEZAK 62-63

SADRŽAJ

EDITORIAL

Vida Demarin

DOI: 10.21857/9xn31cd1wy

It is with honor and delight to anounce our new EDITOR EMERITUS. Our longstanding editor in chief professor Marko Pećina, after number of years of successful leading of our journal, has been elected to the new position EDITOR EMERITUS. During many years under professor Pećina's leadership, our journal has developed to a highly respectable journal, offering to estimated readers as well as to authors, a vivid, international scientific platform for interchange of ideas and reserch results, and for its clinical translation. Professor Pećina, at his new position, will continue his inspiring work futher on, giving us, with his knowledge and experience, wisdom and strength for the future. With sincere respect and gratitude we are looking forward to our tight, future collaboration.

In this volume of RAD there are again a number of interesting papers, case-reports and interviews, as well as presentations of scientfic activities organized by members of our Department for Medical Sciences.

The Prevalence of prediabetes and risk factors in the general adult population of Croatia- EH-UH 2 study is the first study in which the prevalence of prediabetes and its association with risk factors were determined in a representative randomized sample of the general adult population of Croatia. While further research is needed, the results of this study show that in the presence of multiple risk factors for prediabetes, the focus should be on age, systolic blood pressure and albuminuria as the main predictive factors of prediabetes, especially in individuals with visceral obesity. Professor Bojan Jelakovic and members of his team should be congratulated for this excellent, innovative clinical research. Colleagues from Sarajevo, led by professor Edin Medvjedović and his team presented their interesting results as "Analysis of improving business processes by implementing the lean concept at the level of tertiary healthcare", showing that implementation of the *lean* concept would reduce medical waste, which would positively affect the quality of health care services. Colleagues from Pula Frederic-Ivan Silconi and his colleagues presented their results on the posterior circulation ischaemic stroke in a retrospective analysis from a General Hospital in Pula, pointing out the need for comprehensive clinical evaluation. Anja Mandarić and her colleagues presented their results on the use of intrathecal morphine in total hip arthroplasty and they suggest introducing it as a standard procedure in the treatment of orthopedic patients.

The number of review articles starts by an interesting review on current role of functional magnetic stimulation (FMS) in patients with urinary incontinence after radical prostatectomy written by Tvrtko Hudolin and his colleagues.

Ivana Kolčić wrote a review on Lifestyle medicine – a new promise for shifting the tide of non-communicable diseases. It is followed by Ataxia as an initial presentation of Sporadic Creutzfeld – Jakob disease : an atypical case report and literature review written by Slaven Lasić and his colleagues. Recovery of Recurrent Transient Neurogenic Stuttering due to Functional Neuroplasticity is presented by

Marina Roje Bedeković and Lara Pilepić. A case report on Seizure freedom with vagus nerve stimulation in neurofibromatosis type 1 is presented by Asja Hodžić and her colleagues. Matea Prenc and colleagues described a rare case of multiple unruptured intracerebral aneurysms. A case on repeated intravenous thrombolytic therapy with rt-PA alteplase in the treatment of early recurrent ischemic stroke is presented by Josip Sekovanić and colleagues. A case report on secondary central nervous system involvement in systemic ALK+ anaplastic large cell lymphoma is described by Žana Besser Silconi and her colleagues.

There are also two interesting letters: "Long waiting lists cause a "Vertigo Issue" many health care systems – sight from Croatian perspective" written by Filip Đerke and colleagues and another letter on "Diagnosing Functional Neurological Disorder in Croatia. What can be changed?" by Slaven Lasić and colleagues.

The section NEWS & EDUCATION starts with the presentation of the book authored by Željko Cvetnić, full member of Department of Medical Sciences of CASA "Povijest tuberkuloze s osvrtom na asanaciju i tuberkulozu u Mraclinu. Then, there are

presentations on scientific events organized by members of our Department of Medical Sciences, followed by ESSAYS with two interviews.

Dear colleagues, we do hope that you will enjoy reading the content of this volume and finding interesting information, what could possible inspire you to prepare your own contribution to be published in the next issue of our journal.

Prevalence of prediabetes and risk factors in the general adult population of Croatia - EH-UH 2 study

Luka Prgomet[1], Juraj Skelin[1], Marija Domislović[2], Bojan Jelaković[1,2]

[1] School of Medicine, University of Zagreb
[2] University Hospital Zagreb, Department for Nephrology, Hypertension, Dialysis and Transplantation

Abstract:

Introduction: Prediabetes is a state of elevated blood glucose, but not high enough to be classified as diabetes. The prevalence depends on the criteria used in the definition of prediabetes and on the observed populations. Known risk factors are obesity, age ≥ 45 years, positive family history of type 2 diabetes, insufficient physical activity, arterial hypertension, dyslipidaemia, and positive smoking status. The aim of our study was to determine the prevalence of prediabetes in a randomized, representative sample of the adult population of the Republic of Croatia and to determine the association and predictability of risk factors.

Materials and methods: Out of 1219 adult participants who were involved in the scientific research project EHUH-2, 687 met the final criteria. All participants underwent clinical examination. Personal and family history were obtained from the collected data in the questionnaire. The participants were instructed to fast for 12 hours before the blood draw and were given detailed instructions on collecting a 24-hour urine sample. According to the ADA criteria, prediabetes is defined as a fasting glucose value between 5.6, and 6.9 mmol/L.

Results: The prevalence of prediabetes in our sample was 11.1%. Predictive factors for prediabetes were older age, male gender, higher body weight, higher body mass index, larger waist circumference, higher systolic and diastolic blood pressure, larger body surface area, a higher percentage of visceral fat, decreased glomerular filtration rate, higher serum uric acid levels, and greater albuminuria (ACR). The final hierarchical regression model, which included body mass index, systolic and diastolic blood pressure, waist circumference, age, gender, eGFR, information on smoking, albuminuria, and urate, was statistically significant (p < ; 0.001; Nagelkerke R2=0,272).

Conclusion: Our study is the first in which the prevalence of prediabetes and its association with risk factors were determined in a representative randomized sample of the general adult population of Croatia. While further research is needed, our results shows that in the presence of multiple risk factors for prediabetes, the focus should be on age, systolic blood pressure, and albuminuria as the main predictive factors of prediabetes, especially in individuals with visceral obesity.

Keywords: prediabetes, prevalence, predictors, hierarchical regression analysis

Sažetak:

Prevalencija predijabetesa i čimbenici rizika u općoj odrasloj populaciji Hrvatske - EH-UH 2 studija

Uvod: Predijabetes je stanje povišene razine glukoze u krvi, ali nedovoljno visoke da se klasificira kao dijabetes. Učestalost ovisi o kriterijima koji se koriste u definiciji predijabetesa i promatranim populaci-

OPEN ACCESS

Correspondence:
Bojan Jelaković
jelakovicbojan@gmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 20 April 2023
Accepted: 28 May 2023
Published: 26 June 2023

Citation:
Prgomet L, Skelin J, Domislović M, Jelaković B. Prevalence of prediabetes and risk factors in the general adult population of Croatia - EH-UH 2 study 556=62-63 (2023): 10-33
DOI: 10.21857/mzvkptl7l9

jama. Poznati faktori rizika su pretilost, dob ≥ 45 godina, pozitivna obiteljska anamneza dijabetesa tipa 2, nedovoljna tjelesna aktivnost, arterijska hipertenzija, dislipidemija i pušenje. Cilj ovoga istraživanja bio je odrediti učestalost predijabetesa u randomiziranome, reprezentativnom uzorku odrasle populacije Republike Hrvatske te utvrditi povezanost i prediktivnost faktora rizika.
Materijali i metode: U znanstveno istraživačkome projektu EHUH-2 sudjelovalo je 1219 odraslih sudionika, od kojih je 687 ispunjavalo konačne kriterije. Svi sudionici su prošli klinički pregled. Osobna i obiteljska anamneza dobiveni su iz prikupljenih podataka u upitniku. Ispitanici su bili upućeni da budu 12 sati natašte prije pregleda na kojem je izvršeno vađenje krvi, te gdje su dobili detaljne upute kako skupiti 24-satnu mokraću. Prema kriterijima Američke udruge za dijabetes (ADA), predijabetes se definira kao vrijednost glukoze natašte između 5,6 i 6,9 mmol/L.
Rezultati: Prevalencija predijabetesa u našem uzorku iznosila je 11,1%. Prediktivni faktori za predijabetes uključuju stariju dob, muški spol, veću tjelesnu težinu, veći indeks tjelesne mase, veći opseg struka, viši sistolički i dijastolički arterijski tlak, veću površinu tijela, veći postotak visceralne masti, smanjenu glomerularnu filtraciju, višu razinu serumske mokraćne kiseline te veću albuminuriju (ACR). Završni hijerarhijski regresijski model u koji su ušli indeks tjelesne mase, sistolički i dijastolički arterijski tlak, opseg struka, dob, spol, eGFR, podatak o pušenju, albuminurija i urati bio je statistički značajan ($p < 0,001$; Nagelkerke $R2=0,272$).
Zaključak: Naša studija je prvo istraživanje na reprezentativnome randomiziranom uzorku opće odrasle populacije Hrvatske u kojem je određena učestalost predijabetesa i njegova povezanost s faktorima rizika. Iako su potrebna daljnja istraživanja, naš model ima kliničke implikacije jer pokazuje da u prisutnosti više faktora rizika za predijabetes, treba obratiti pozornost na dob, sistolički arterijski tlak i albuminuriju kao glavne prediktivne faktore predijabetesa, posebno kod osoba s visceralnom pretilošću.

Ključne riječi: predijabetes, prevalencija, prediktori, hijerarhijska regresijska analiza

Introduction

Prediabetes is a metabolic disorder characterized by impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) that can potentially progress to type 2 diabetes. It is described as a state of elevated blood glucose, but not high enough to be classified as diabetes (1). Currently, there is no consensus among international societies and associations on the lower limit of blood glucose as a diagnostic criterion for the onset of prediabetes, which explains the differences in the prevalence of prediabetes obtained in various studies and populations (Figure 1) (2). According to the World Health Organization (WHO), prediabetes is defined as a fasting plasma glucose (FPG) level of 6.1 to 6.9 mmol/L (IFG) or a blood glucose level after an oral glucose tolerance test (OGTT) of 7.8 to 11.0 mmol/L (IGT) (3). The latest guidelines from the American Diabetes Association (ADA) define prediabetes as an FPG between 5.6 and 6.9 mmol/L (IFG), OGTT between 7.8 and 11.0 mmol/L (IGT), or glycated haemoglobin (HbA1c) levels that must be between 5.7% and 6.4% (1). In 2021, the number of adults with prediabetes or IGT worldwide was estimated at 541 million people (10.6%) (Figure 2A), with the assumption that this number will increase to 730 million (11.4%) by 2045 (4). The number of adults with IFG was 319 million (6.2%) (Figure 2B), and it is predicted to increase to 441 million (6.9%) by 2045 (4). In 2019, the number of adults over 18 with prediabetes in the United States was 96 million (38%), and only 19% of them were informed of this by a healthcare provider (5). According to a study conducted in Croatia that included 5092 participants, 17.3% had prediabetes using HbA1c criteria (6). In a study conducted in 2008 using WHO-IFG criteria, the prevalence of prediabetes was 11.3% (7). The prevalence of prediabetes in other European countries varies from country to country depending on the criteria used and the population included. In Italy, the prevalence was 39.9% (ADA-IFG criteria) or 16.4% (WHO-IFG criteria), in the Czech Republic it was 27.8% (ADA-HbA1c criteria), in Slovakia 12.5%, in France 9.9% (WHO-IFG criteria), and 28.6% (ADA-IFG criteria) (8-11). In a meta-analysis from 2016 that used two criteria, the prevalence of prediabetes in Europe was 22.3% (12).

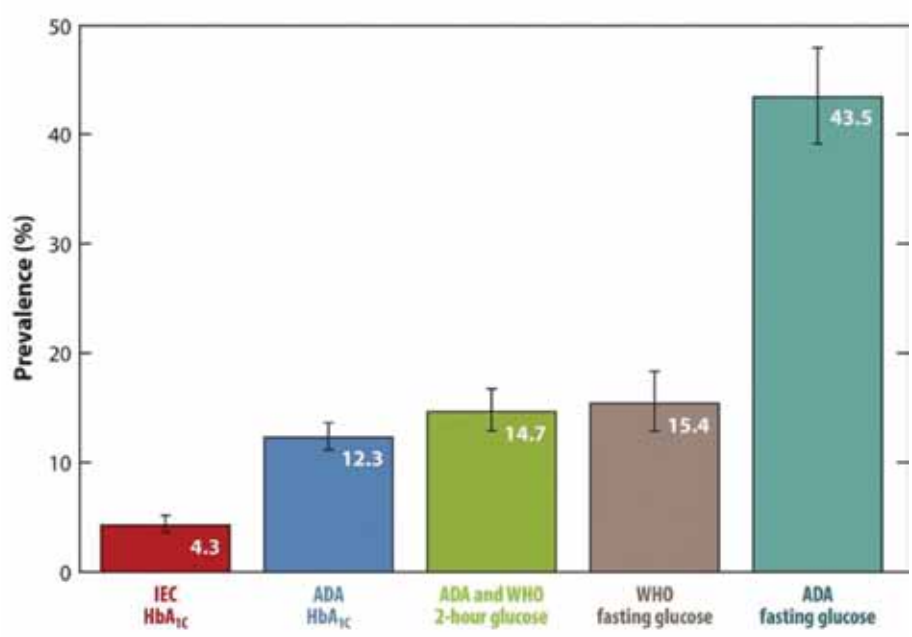


Figure 1. Prevalence of prediabetes in individuals over 20 years old in the US depending on the used definition of prediabetes (adapted from Echouffo-Tchegui, Selvin) (2); IEC: International Expert Committee; ADA: American Diabetes Association; WHO: World Health Organization.

A

B

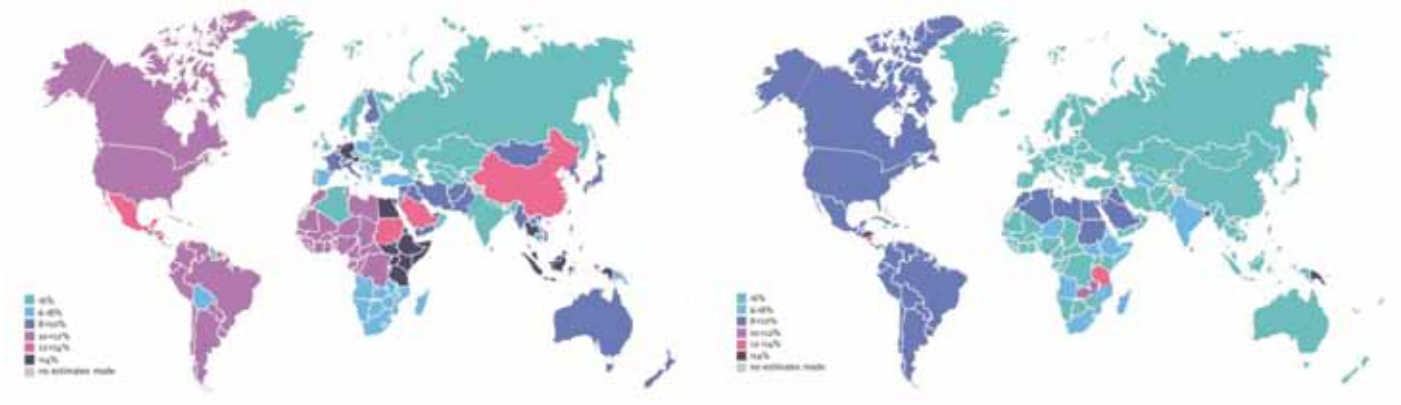


Figure 2. Prevalence of IGT (A) and prevalence of IFG (B) in adults in 2021 according to the International Diabetes Federation. IDF Diabetes Atlas, 10th Ed. Brussels, Belgium: 2021. (4)

Several mechanisms are involved in the pathophysiology of prediabetes. The fundamental disorder of homeostasis is increased insulin resistance, which can be present up to thirteen years before the diagnosis of diabetes (13-19) (Figure 3).

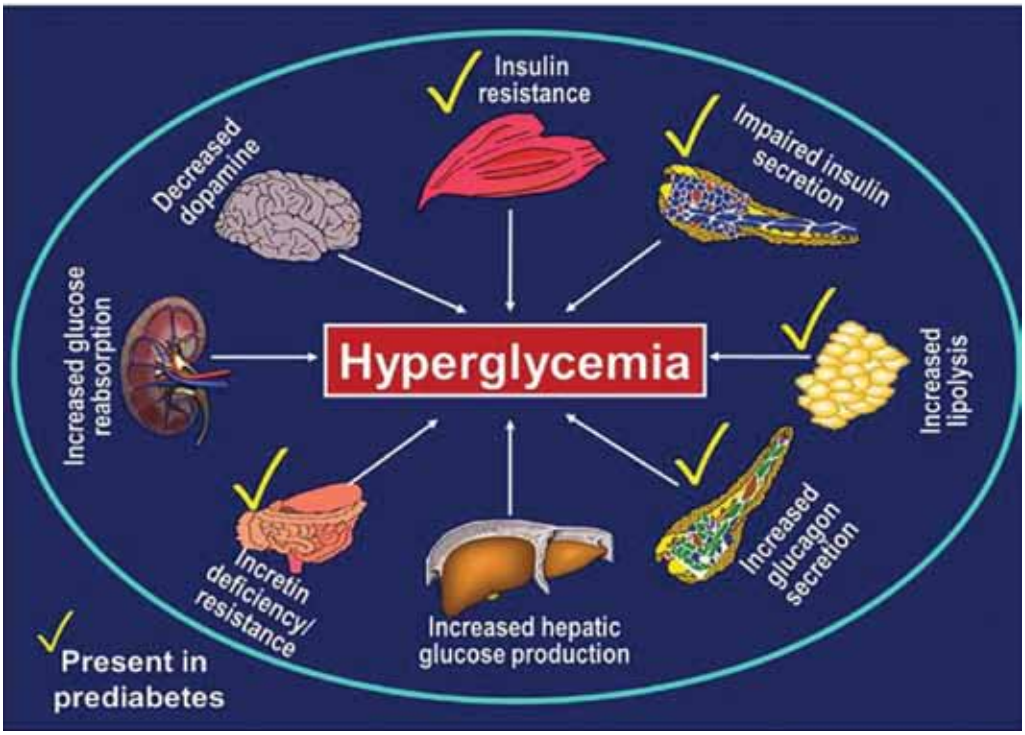


Figure 3. Pathophysiological mechanisms involved in the development of prediabetes and type 2 diabetes (From Dagogo-Jack et al.) (17)

Research has shown that prediabetes increases the risk of developing type 2 diabetes (T2D). The annual incidence of T2D development in prediabetic individuals is estimated at 5 to 10% (20-23). A 2018 meta-analysis including 103 cohort studies concluded that the risk of developing T2D is higher in prediabetic individuals compared to those with normoglycemia by 3.61 to 10.1 times, depending on the definition of prediabetes or IGT (24). Individuals with prediabetes also generally have a high prevalence of cardiovascular risk factors, leading to an increased risk of developing macrovascular complications (Figure 4) (25-28). Prediabetic individuals have an increased risk of developing cardiovascular disease and overall mortality compared to those with normoglycemia (29-31). In addition, there is evidence of a connection between prediabetes and kidney function, peripheral neuropathy, erectile dysfunction, and an increased incidence of cancer (32-38). Risk factors for prediabetes include obesity, age over 45, positive family history of T2D, physical activity less than 3 times per week, gestational diabetes in the past, and polycystic ovary syndrome (39). Risk factors also include hypertension, dyslipidemia, and positive smoking status (Figure 5) (9,25, 40). If not prevented through lifestyle changes, and in some cases treated, prediabetes can lead to various complications (Figure 6) (41).

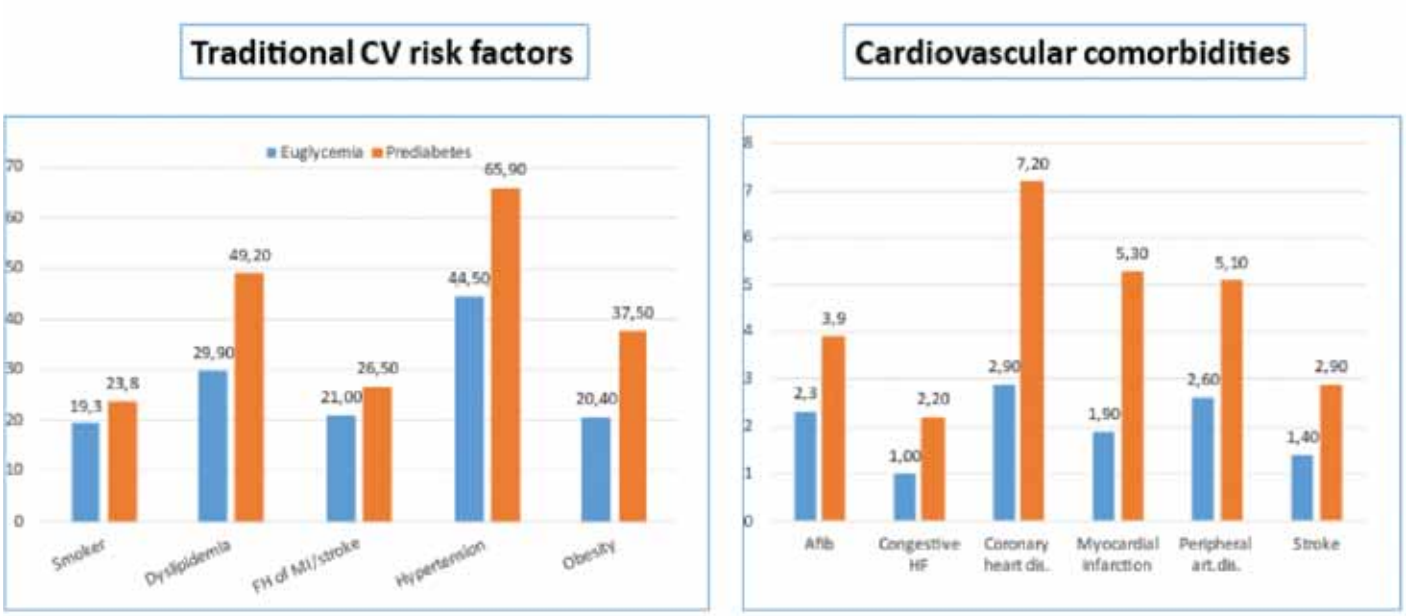


Figure 4. Frequency of cardiovascular risk factors and diseases in individuals with prediabetes; adapted from (25) Afib: atrial fibrillation, MI: myocardial infarction, HF: heart failure

Figure 5. Prediabetes risk factors; according to (25)

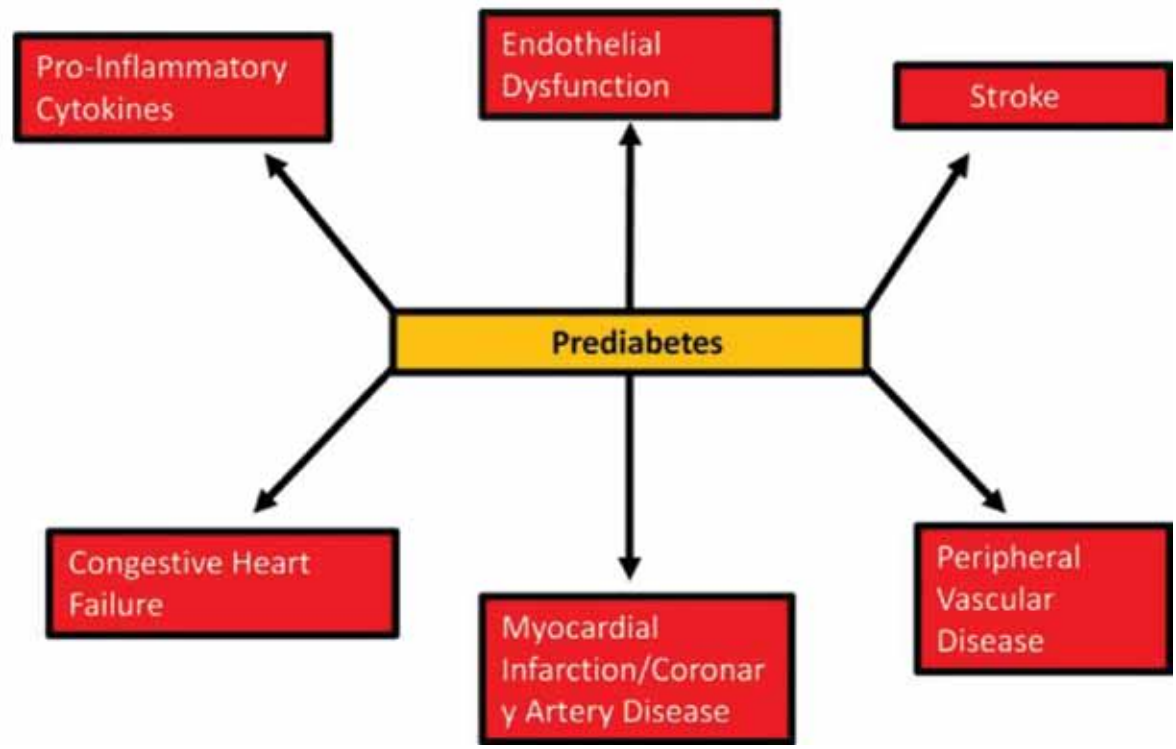


Figure 6. Macrovascular complications associated with prediabetes; from (41)

The presented data indicates a significant public health importance of prediabetes. Therefore, it is crucial to determine the prevalence of prediabetes in each specific population and analyse the risk factors and their predictivity to organize targeted screening and preventive programs. This is precisely one of the goals of the EHUH-2 project, as well as a stimulus for the preparation of this paper. This study aims to determine the prevalence of prediabetes in a randomized representative sample of the adult population of the Republic of Croatia and to analyse the predictive value of risk factors for the onset of prediabetes. The specific objectives are to compare the determined prevalence of prediabetes to the results from the literature, to analyse the characteristics of subjects with prediabetes, and to determine the association between risk factors and prediabetes and the strength of their predictive value for prediabetes.

Materials and Methods

Participants

In this cross-sectional study, 1219 adult participants were involved in the scientific research project EHUH-2. Figure 7 shows a diagram of the study, including the method of participant recruitment and group formation. All participants provided informed consent, underwent clinical examinations, and completed a large, structured questionnaire about their personal and family medical history. The clinical examinations, measurements, and tests were conducted by physicians and medical students involved in the EH-UH 2 project, who had received training to ensure standardized data collection and measurements. The study was approved by the ethics committee of the University of Zagreb School of Medicine.

Methods

All participants underwent clinical examination. Personal and family history, as well as age, were obtained from the collected data in the questionnaire. Height was measured in a standing position without shoes and expressed in centimeters, while body weight was measured using an Omron BF-511 scale without clothes and expressed in kilograms. Body mass index (BMI) was calculated as the ratio of body weight in kilograms to the square of height in meters. The percentage of body fat and muscle tissue, visceral fat, and basal metabolism were obtained by measur-

ing with the Omron BF-511 scale. In accordance with recent guidelines, arterial blood pressure (BP) was measured with an appropriate-sized Omron M6 oscillometric device. **Definitions:** Prediabetes was defined as a fasting glucose level between 5,6 and 6,9 mmol/L. Diabetes was defined as a positive history and/or antidiabetic therapy and/or fasting glucose level >7 mmol/L. Arterial hypertension (AH) was defined as a positive history and/or BP ≥ 140/90 mmHg and/or use of antihypertensive therapy. Pack years in current or former smokers were calculated as the number of cigarette packs smoked per day multiplied by the duration of smoking in years. Body surface area (BSA) was measured by the Moesteller formula using weight and height. After the measurements and completion of the questionnaire, a fasting blood sample was taken from the participants. Daily salt intake was determined from a 24-hour urine sample based on daily sodium excretion. The participants were instructed to fast for 12 hours prior to the blood draw and were given detailed instructions on how to collect a 24-hour urine sample. All laboratory analyses were performed at the central laboratory at the University Hospital Centre Zagreb. The following measurement methods were used to determine the biochemical parameters: uric acid: photometry with uricase and ascorbate oxidase standardized to ID/MS; instrument: Cobas c 501, Roche; creatinine: enzymatic with creatinine standardized to ID/MS, instrument: Cobas c 501, Roche; glucose: UV photometry with hexokinase standardized to ID/MS, instrument: Cobas c 501, Roche; cholesterol: photometry with cholesterol oxidase (CHOD-PAP) standardized to ID/MS, instrument: Cobas c 501, Roche; triglycerides: photometry with glycerol phosphate oxidase (GPO-PAP) standardized to ID/MS, instrument: Cobas c 501, Roche; HDL-cholesterol: enzymatic homogeneous with modified polyethylene glycol (PEG) and alpha-cyclodextran sulfate standardized to CDC reference method, instrument: Cobas c 501, Roche; LDL-cholesterol: homogeneous enzymatic colorimetry or calculated using Friedewald formula if triglyceride concentration is less than 4 mmol/L and chylomicrons are absent, instrument: Cobas c 501, Roche; albumin: nephelometry standardized with primary ERM DA470 calibrator and secondary Master calibrator, instrument: BN Prospec nephelometer, Siemens.

The basis for data collection is a structured questionnaire consisting of information about the researcher, basic information about the respondent, information about previous illnesses, medications, habits, information about home and outpatient visits, laboratory values, and a questionnaire for physicians. All data were entered into Microsoft Excel (Microsoft, USA), cleaned, and stored in a database. Statistical analysis was performed using SPSS v.29 (IBM Corp., USA). Adequate statistical methods were used in the data analysis. The normality of continuous variables was tested using kurtosis and skewness. Measures of central tendency used to display the variables were the mean and standard deviation, as well as the median and interquartile range. Normally distributed variables were compared using Student's t-test, and the Mann-Whitney test was used for variables with a non-normal distribution. Differences between three or more groups were tested using analysis of variance (ANOVA) and the Kruskal-Wallis test. Categorical variables will be displayed as absolute numbers and proportions. Fisher's exact $\chi 2$ test was used to compare categorical variables. Correlations were tested using Pearson's and Spearman's tests. The value of these tests' ranges from $-1 \leq r \leq +1$, where the sign (-) of the correlation indicates a negative (inverse) correlation, while the sign (+) indicates a positive correlation. The higher the correlation value, the more significant the correlation between variables. The associations of multiple independent variables with a single dependent continuous variable were examined using linear regression, and logistic regression was used for categorical variables. The effect size in logistic regression was the odds ratio (OR) with a 95% confidence interval (95% CI). Hosmer-Lemeshow's test was used as a measure of goodness-of-fit, and the regression coefficient was used as a measure of predictiveness. Hierarchical regression analysis was used to develop predictive models. Nagelkerke's R2 was used as a measure of the proportion of explained variance in the model. Prevalence was used as an indicator of the frequency of prediabetes in the population. A significant level of p-value less than 0.05 was used.

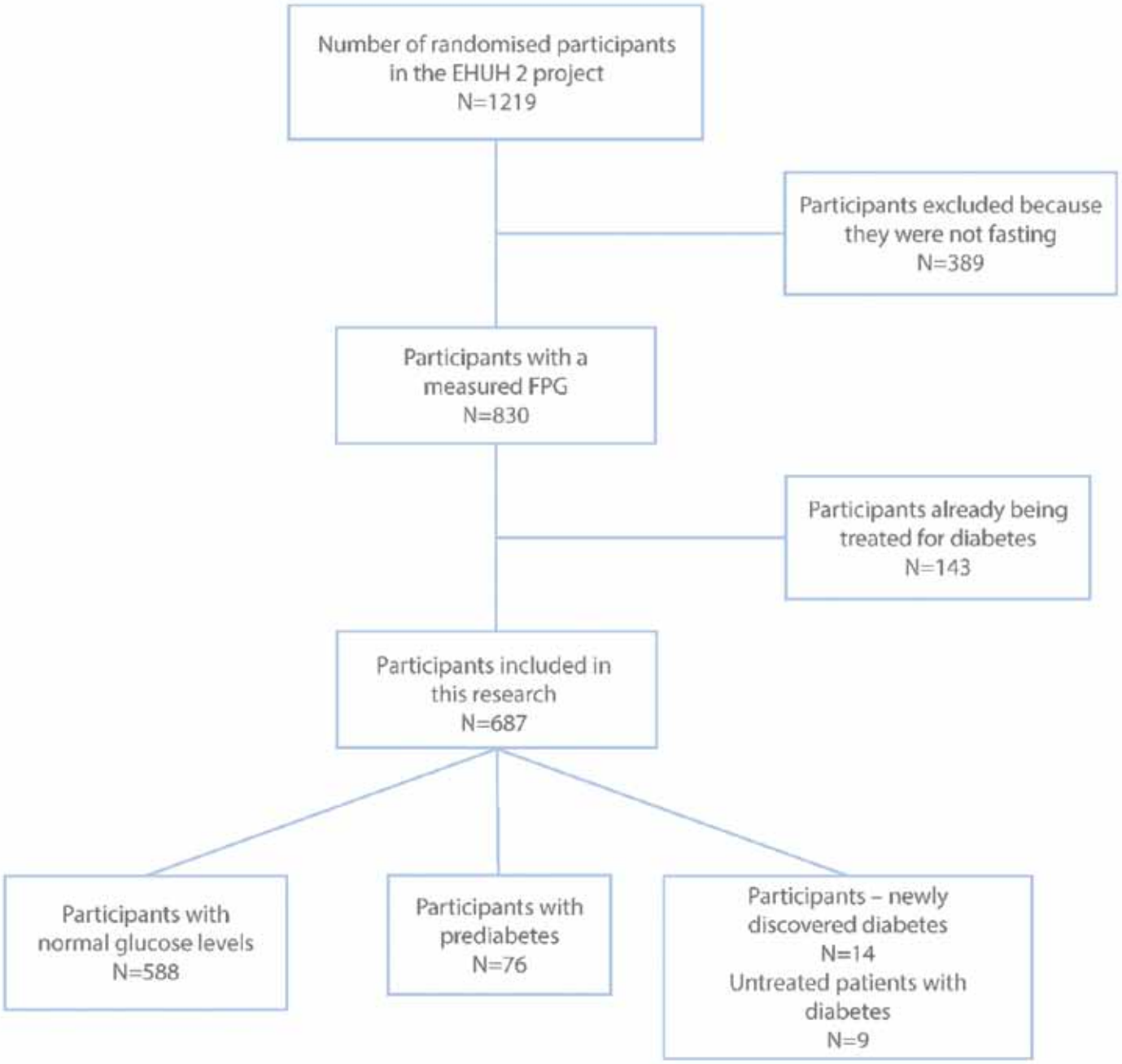


Figure 7. Flow chart showing methods of inclusion, exclusion and the formation of groups

Results

In our group with an average age of 56 ± 15 years, 33.9% were men. The prevalence of prediabetes was 11.1%. The prevalence was significantly higher in men than in women (15% vs. 9%; p < 0,001) (Figure 8). The characteristics of the participants classified by sex are shown in Supplementary Tables 1 and 2. Table 1 shows the characteristics of the participants classified based on their fasting blood glucose levels. Table 2 shows the results of Spearman's correlation between predictor variables and prediabetes status. Results of the univariate-binary logistic regression analysis are shown in table 3. Table 4 shows nine models of hierarchical regression analysis. Variables were entered into the hierarchical model in the order shown in Table 4. All models were statistically significant compared to the null model.

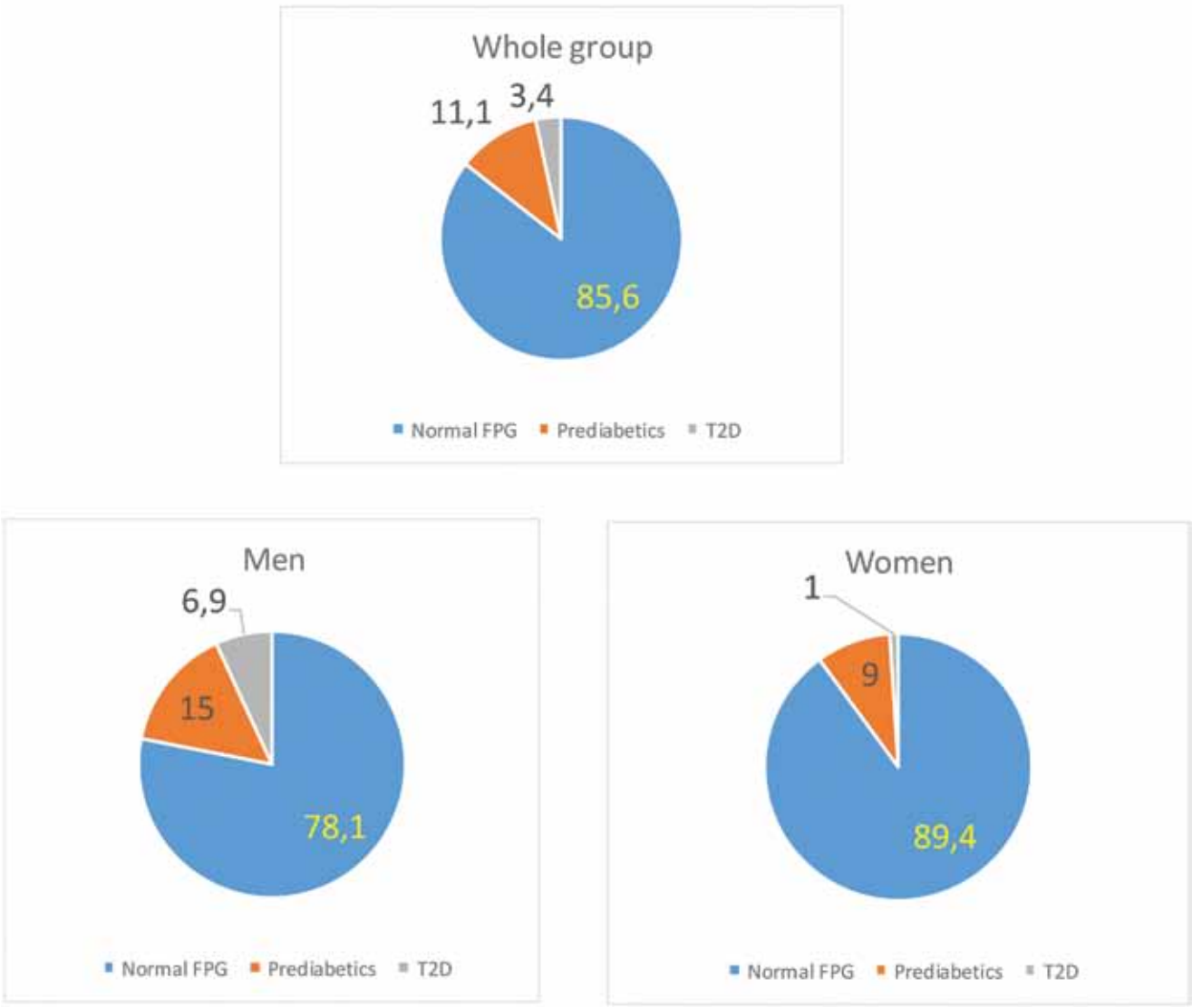


Figure 8. Prevalence of prediabetes in the whole group, and specifically in women and men; FPG: fasting plasma glucose; T2D: type 2 diabetes

Table 1. Demographic and clinical characteristics of participants classified according to FPG [1]

	Individuals with normal glucose values	Prediabetics	Untreated individuals with diabetes	p-value	Post hoc
% (n)	85,6 (588)	11,1 (76)	3,3 (23)	-	-
Men, % (n)	31 (182)	46,1 (35)	69,6 (16)	-	
Age (years)	54,51 ± 14,45	65,59 ± 10,58	66,78 ± 10,44	<0,001	a:b – p = <0,001; a:c – p = <0,001; b:c – p = 0,882
Height (cm)	166,56 ± 9,47	166,83 ± 9,20	170,26 ± 8,98	0,182	
Weight (kg)	79,11 ± 17,08	85,22 ± 13,41	85,86 ± 19,04	0,003	a:b – p = 0,012; a:c – p = 0,168; b:c – p = 0,987
BSA Moesteller (m^2)	1,90 ± 0,22	1,98 ± 0,19	2 ± 0,24	0,001	a:b – p = 0,009; a:c – p = 0,086; b:c – p = 0,924
BMI (kg/m^2)	28,34 ± 5,08	30,68 ± 4,44	28,75 ± 5,18	<0,001	a:b – p = <0,001; a:c – p = 0,931; b:c – p = 0,285
BMI categories					
BMI, <25 % (n)	28,5 (161)	6,7 (5)	9,1 (2)	<0,001	a:b – p = <0,001; a:c – p = 0,048; b:c – p = 0,405
BMI, 25 – 30 % (n)	35,9 (203)	45,3 (34)	59,1 (13)		
BMI, >30 % (n)	35,6 (202)	48 (36)	31,8 (7)		
Waist circumference (cm)	94,19 ± 14,08	100,81 ± 13,42	109,13 ± 14,14	<0,001	a:b – p = 0,002; a:c – p = <0,001; b:c – p = 0,117
SBP (mmHg)	131,49 ± 17,08	143,79 ± 18,2	143,13 ± 25,63	<0,001	a:b – p < 0,001; a:c – p = 0,100; b:c – p = 1,000
DBP (mmHg)	82,43 ± 9,69	85,76 ± 11,79	83,44 ± 13,95	0,026	a:b – p = 0,054; a:c – p = 0,937; b:c – p = 0,751
HR (bpm)	73,48 ± 10,8	74,71 ± 13,23	75,88 ± 10,8	0,424	
Body fat (%)	36,27 ± 9,46	37,27 ± 10,45	34,69 ± 12,37	0,587	
Muscle mass (%)	26,6 (23,8 – 30,5)	26,2 (23,2 – 31,3)	30 (23,4 – 32,9)	0,507	
BMR (kkcal)	1573,42 ± 248,53	1642,34 ± 212,95	1752 ± 223,31	0,003	a:b – p = 0,105; a:c – p = 0,021; b:c – p = 0,292
Visceral fat (%)	10,29 ± 4,41	13,86 ± 4,71	14,47 ± 3,29	<0,001	a:b – p = <0,001; a:c – p = 0,002; b:c – p = 0,892
Serum creatinine (umol/L)	70 (62 – 81)	76,5 (65,5 – 84,5)	86 (78 – 100)	<0,001	a:b – p = 0,011; a:c – p = <0,001; b:c – p = 0,009
CKD Epi (ml/min/1,73 m^2)	90,13 ± 17,69	80,36 ± 16,32	71,63 ± 25,7	<0,001	a:b – p = <0,001; a:c – p = 0,006; b:c – p = 0,289
CKD Mi (ml/min)	98,66 ± 22,86	94,22 ± 22	85,83 ± 34,51	0,024	a:b – p = 0,285; a:c – p = 0,250; b:c – p = 0,569
Urate levels (mmol/L)	282,68 ± 77,5	327,38 ± 75,56	356,59 ± 87,84	<0,001	a:b – p = <0,001; a:c – p = <0,001; b:c – p = 0,300
Total cholesterol (mmol/L)	5,3 ± 1,08	5,38 ± 1,32	5,3 ± 1,41	0,847	
Triglyceride (mmol/L)	1,19 (0,86 – 1,65)	1,25 (0,98 – 1,84)	1,34 (1,07 – 1,8)	0,05	a:b – p = 0,045; a:c – p = 0,127; b:c – p = 0,698
HDL cholesterol (mmol/L)	1,49 ± 0,39	1,45 ± 0,38	1,31 ± 0,5	0,088	
LDL cholesterol (mmol/L)	3,22 ± 0,99	3,28 ± 1,22	3,16 ± 1,19	0,847	
Sodium/potassium ratio	3,35 ± 1,32	3,12 ± 1,41	4,30 ± 1,51	0,002	a:b – p = 0,391; a:c – p = 0,006; b:c – p = 0,002
Daily salt intake (grams)	9,74 ± 4,69	9,49 ± 4,46	12,46 ± 5,43	0,028	a:b – p = 0,912; a:c – p = 0,002; b:c – p = 0,038

Table 1. Characteristics of participants classified according to FPG - continuation

Duration of hypertension (years)	9 (4 – 14)	10 (5 – 17)	14 (3 – 29,5)	0,376
AH yes, % (n)	47,4 (275)	74 (54)	76,2 (16)	<0,001
CKD yes, % (n)	2,5 (14)	5,4 (4)	9,1 (2)	0,096
Smokers, % (n)	28,1 (165)	27,3 (18)	17,4 (4)	0,404
PY	12 (5 – 25)	24 (8 – 40)	50 (12,5 – 75)	<0,001
Exercise intensity				
Low, % (n)	44,9 (264)	52,6 (40)	60,9 (14)	0,032
Medium, % (n)	35,9 (211)	19,7 (15)	26,1 (6)	
I don't know, % (n)	19,2 (113)	27,6 (21)	13 (3)	

[1]Continuous variables are expressed as mean ± SD for normally distributed variables and as median and interquartile range for non-normally distributed variables. Categorical variables are presented as percentages (number).
BSA: body-surface area; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; bpm: beats pre minute; BMR: basal metabolic rate; CKD EPI: Chronic Kidney Disease Epidemiology Collaboration; CKD EPI Mi: CKD EPI equation adjusted for individual body surface area calculated using the Mosteller equation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AH: arterial hypertension; CKD: chronic kidney disease; PY: pack-years.

Table 2. Statistically significant results of Spearman correlation between predictor variables and prediabetes status[a]

Independent variable	Correlation coefficient	p-value	95% CI
Age (years)	0,253	< 0,001	0,178 – 0,325
Average personal monthly income	-0,079	0,042	-0,156 – (-0,001)
Average family monthly income	-0,082	0,034	-0,160 – (-0,004)
Pack years	0,177	0,002	0,061 – 0,289
Weight (kg)	0,147	< 0,001	0,069 – 0,224
BMI (kg/m^2)	0,163	< 0,001	0,085 – 0,240
BSA Moesteller (m^2)	0,130	< 0,001	0,051 – 0,208
Waist circumference (cm)	0,168	< 0,001	0,077 – 0,257
SBP (mmHg)	0,206	< 0,001	0,129 – 0,280
DBP (mmHg)	0,121	0,002	0,042 – 0,198
BMR (kkcal)	0,122	0,006	0,032 – 0,210
Visceral fat (%)	0,254	< 0,001	0,167 – 0,336
Serum creatinine (mmol/L)	0,099	0,011	0,021 – 0,176
CKD Epi (ml/min/1,73m^2)	-0,178	< 0,001	-0,253 – (-0,101)
Serum Urate (mmol/L)	0,183	< 0,001	0,106 – 0,258
Triglycerides (mmol/L)	0,078	0,045	0,000 – 0,155
ACR	0,114	0,006	0,031 – 0,196

BMI: body mass index; BMR: basal metabolic rate; BSA: body surface area; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMR: basal metabolism rate; CKD EPI: Chronic kidney disease epidemiology collaboration; ACR: albumin-to-creatinine ratio; CI: confidence interval

Table 3. Univariate binary logistic regression analysis[a]

	ß	p-value	OR	95% CI
Sex	-0,644	0,009	0,525	0,324 – 0,852
Age (years)	0,062	< 0,001	1,064	1,043 – 1,085
BMI (kg/m^2)	0,088	< 0,001	1,092	1,042 – 1,144
BMI categories:				
BMI 25-30 (kg/m^2)*	1,686	< 0,001	5,393	2,062 – 14,103
BMI ≥30 (kg/m^2)*	1,,747	< 0,001	5,739	2,202 – 14,958
BSA Moesteller (m^2)	1,690	0,002	5,422	1,820 – 16,152
Waist circumference (cm)	0,035	< 0,001	1,035	1,015 – 1,056
Weight (kg)	0,020	0,004	1,020	1,006 – 1,033
BMR (kkcal)	0,001	0,036	1,001	1,000 – 1,002
Visceral fat (%)	0,158	< 0,001	1,171	1,106 – 1,239
SBP (mmHg)	0,035	< 0,001	1,035	1,022 – 1,049
DBP (mmHg)	0,033	0,007	1,034	1,009 – 1,059
SBP categories	1,385	< 0,001	3,994	2,429 – 6,565
DBP categories	0,731	0,006	2,077	1,238 – 3,484
Serum creatinine (mmol/L)	0,015	0,025	1,015	1,002 – 1,028
CKD Epi (ml/min/1,73 m^2)	-0,030	< 0,001	0,971	0,958 – 0,984
Serum urate (mmol/L)	0,007	< 0,001	1,007	1,004 – 1,010
ACR	0,002	0,037	1,002	1 – 1,003
PY	0,028	< 0,001	1,029	1,013 – 1,045
AH	1,148	< 0,001	3,152	1,823 – 5,450
Physical activity	-0,757	0,017	0,469	0,252 – 0,873
Average personal monthly income	-0,569	0,025	0,566	0,345 – 0,931

[a]Sex: male vs. female; SBP categories: <140 vs. >140; DBP categories: <90 vs. >90; Arterial hypertension: yes vs. no; Physical activity: low vs. moderate; Average personal monthly income: <3500 vs. >3500 BMI: body mass index; BSA: body surface area adjusted for individual values calculated using the Mosteller equation; SBP: systolic blood pressure; DBP: diastolic blood pressure; CKD EPI: Chronic kidney disease epidemiology collaboration; ACR: albumin-to-creatinine ratio; PY: pack-years; AH: arterial hypertension; OR: odds ratio; CI: confidence interval
*In relation to BMI <25 kg/m2

Table 4. Hierarchical regression models for prediabetes prediction

		ß	p-value	OR	95% CI	p-value	Nagelkerke R^2
Model 1	BMI (kg/m2)	0,083	0,003	1,086	1,028 – 1,147	0,003	0,038
Model 2	BMI (kg/m2)	-0,031	0,526	0,970	0,882 – 1,066	< 0,001	0,073
	Waist circumference (cm)	0,054	0,005	1,056	1,017 – 1,096		
Model 3	BMI (kg/m2)	-0,001	0,979	0,999	0,907 – 1,1	< 0,001	0,199
	Waist circumference (cm)	0,035	0,072	1,036	0,997 – 1,076		
	Age (years)	0,069	< 0,001	1,072	1,044 – 1,101		
Model 4	BMI (kg/m2)	0,049	0,378	1,050	0,942 – 1,17	< 0,001	0,215
	Waist circumference (cm)	0,011	0,618	1,011	0,968 – 1,056		
	Age (years)	0,074	0,000	1,076	1,047 – 1,106		
	Sex	-0,728	0,044	0,483	0,238 – 0,979		
Model 5	BMI (kg/m2)	0,039	0,480	1,040	0,933 – 1,16	< 0,001	0,227
	Waist circumference (cm)	0,012	0,606	1,012	0,968 – 1,057		
	Age (years)	0,066	< 0,001	1,068	1,039 – 1,099		
	Sex	-0,643	0,079	0,526	0,256 – 1,078		
	SBP (mmHg)	0,016	0,079	1,016	0,998 – 1,034		
Model 6	BMI (kg/m2)	0,037	0,515	1,038	0,928 – 1,161	< 0,001	0,231
	Waist circumference (cm)	0,013	0,574	1,013	0,968 – 1,06		
	Age (years)	0,060	< 0,001	1,062	1,031 – 1,094		
	Sex	-0,677	0,068	0,508	0,245 – 1,051		
	SBP (mmHg)	0,025	0,042	1,025	1,001 – 1,05		
	DBP (mmHg)	-0,024	0,265	0,976	0,935 – 1,019		
Model 7	BMI (kg/m2)	0,036	0,529	1,037	0,926 – 1,161	< 0,001	0,232
	Waist circumference (cm)	0,013	0,568	1,013	0,968 – 1,061		
	Age (years)	0,055	0,004	1,056	1,018 – 1,096		
	Sex	-0,682	0,067	0,506	0,244 – 1,048		
	SBP (mmHg)	0,025	0,039	1,026	1,001 – 1,051		
	DBP (mmHg)	-0,024	0,285	0,977	0,935 – 1,02		
	CKD Epi (ml/min/1,73 m2)	-0,005	0,653	0,995	0,973 – 1,017		

Table 4. Hierarchical regression models for prediabetes prediction - continued

Model 8	BMI (kg/m2)	0,053	0,358	1,055	0,941 – 1,182	< 0,001	0,262
	Waist circumference (cm)	0,005	0,816	1,005	0,96 – 1,053		
	Age (years)	0,055	0,005	1,056	1,017 – 1,098		
	Sex	-0,679	0,074	0,507	0,24 – 1,068		
	SBP (mmHg)	0,026	0,038	1,027	1,001 – 1,053		
	DBP (mmHg)	-0,021	0,344	0,979	0,937 – 1,023		
	CKD Epi (ml/min/1,73 m2)	-0,007	0,567	0,993	0,971 – 1,016		
	Smoking status	0,673	0,079	1,960	0,924 – 4,156		
	ACR	0,003	0,043	1,003	1 – 1,005		
Model 9	BMI (kg/m2)	0,034	0,564	1,035	0,921 – 1,163	< 0,001	0,272
	Waist circumference (cm)	0,006	0,811	1,006	0,961 – 1,053		
	Age (years)	0,058	0,003	1,059	1,02 – 1,101		
	Sex	-0,484	0,229	0,616	0,28 – 1,356		
	SBP (mmHg)	0,027	0,034	1,027	1,002 – 1,053		
	DBP (mmHg)	-0,023	0,295	0,977	0,936 – 1,02		
	CKD Epi (ml/min/1,73 m2)	0,002	0,900	1,002	0,977 – 1,027		
	Smoking status	0,691	0,073	1,995	0,937 – 4,246		
	ACR	0,003	0,042	1,003	1 – 1,005		
	Serum urate (mmol/L)	0,004	0,119	1,004	0,999 – 1,009		

[a]BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CKD EPI: Chronic kidney disease epidemiology collaboration; ACR: albumin-to-creatinine ratio; OR: odds ratio; CI: confidence interval

Discussion

This is the first prevalence study of prediabetes and its association with risk factors in a randomized sample of the general adult population in Croatia. The obtained data on the high prevalence of prediabetes and its significant association with several important risk factors indicate the need for prediabetes screening, especially in the part of the population with a high risk of prediabetes, and the necessity of systematic and permanent education of the population about the importance of changing bad lifestyle habits. The prevalence of prediabetes in our study was 11.1%, while the estimate for the entire world in the IDF Atlas was 6.2%, and for Croatia, it was 7.1% (4,42). This difference is likely due to the use of different criteria for diagnosing prediabetes, in addition to the differences in the characteristics of the populations included in the studies. In our study, we used the definition of prediabetes as a fasting blood glucose level between 5.6 and 6.9 mmol/L (IFG-ADA criteria), while the IDF Atlas used the WHO definition of fasting glucose levels between 6.1 and 6.9 mmol/L (IFG-WHO criteria). From studies that used only the IFG-ADA criteria, the prevalence of prediabetes was 12.5% in Slovakia, which is consistent with our results, while the prevalence was significantly higher in France (28.6%) and Italy (39.9%) (8, 10, 11). When comparing the prevalence of prediabetes of 11.1% obtained for our population with the results obtained in other countries that used IFG-WHO criteria, our results are in line with those obtained in France (9.9%), lower than the results obtained in Italy (16.4%), and higher than the results obtained in Hungary (4.4%) (8, 11, 43). Our results are consistent with previous reports for Croatia (11.3%) when the same criteria were used, but the prevalence is lower when compared to the data based on the criterion that includes HbA1C (17.3%) (6, 7). However, in addition to the differences in the criteria used, the higher prevalence in this other study conducted in Croatia may be explained by differences between the groups because that study did not analyse data obtained from a randomized sample of the general population, but included patients who were admitted to the emergency department or were examined by their family physicians. It is important to note that using only one of the three criteria stated by ADA or one of the two criteria stated by WHO is likely to underestimate the prevalence of prediabetes, as there are participants for whom one criterion may be negative while other criteria may be positive. This is evident from the results of a study conducted in Germany, where the prevalence of prediabetes was 33% according to the fasting glucose criterion, 16% according to the OGTT criterion, 26% according to the elevated HbA1c criterion, and when any of the three criteria were used, the prevalence was as high as 50% (44). However, it should be noted that the study only considered participants over the age of 37, which undoubtedly influenced the results, as it is well-known that the prevalence of prediabetes increases with age. Differences in the prevalence of prediabetes were also observed in a large European meta-analysis depending on the criteria used, i.e., definitions (12). The prevalence of prediabetes was 8.4% when using the IFG-WHO criterion and 11.4% when using the OGTT criterion, while the overlap was only 2.5%, which could indicate a true prevalence of around 22% (12). It is important to note that our results are also consistent with these data. A screening test must be simple, accessible, sensitive, and inexpensive because it is necessary to examine a large number of people to identify a small number of potential cases that must be subsequently confirmed with more specific diagnostic tests. In this study, we decided to use the IFG-ADA criteria, i.e., fasting glucose level, which we chose because it is very simple, accessible, and cheap. We are aware that it is not as sensitive as, for example, OGTT or HbA1C, which are, however, more demanding, and expensive for screening in the general population. To increase sensitivity, we opted for IFG-ADA rather than IFG-WHO criteria due to the wider range that includes subjects with lower fasting glucose values. This sample of the general adult population in Croatia, with older average age, a high frequency of hypertension, dyslipidemia, smokers, and obesity, is at high risk for developing prediabetes. The average BMI in prediabetics was 30.68 kg/m2, and only 6.7% of prediabetics had a BMI < 25 kg/m^2. Similar characteristics of prediabetics are described in various studies, such as those from Romania and Spain (45, 46). Using univariate binary logistic regression analysis, we examined the association of various risk factors with prediabetes status. Age, body weight, BMI, waist circumference, and hypertension were risk factors that showed a statistically significant positive correlation with prediabetes in our study. These are risk factors that have also been shown to be significant in other studies (40). The Czech cross-sectional study from 2014 and the German KORA (Cooperative Health Research in the Region of Augsburg) study also showed statistical significance for age, BMI, and waist circumference (9, 44), while SBP and DBP were not measured. Gender in the Czech study was not significant, while it showed a statistically significant effect on prediabetes in the German study. Our analysis also found that hypertension has a statistically significant effect on prediabetes, which has been shown in many studies (9, 40, 44, 47). All of the aforementioned risk factors, except waist circumference, are considered general risk factors for cardiovascular diseases and are included as such in numerous cardiovascular risk calculators. Thus, our study confirms that prediabetes, type 2 diabetes, and cardiovascular diseases share many similar risk factors that are crucial in the pathophysiology of these diseases. The American cross-sectional study conducted on a sample of MESA (Multi-Ethnic Study of Atherosclerosis) in 2015 showed that individuals with prediabetes in a population without previously known cardiovascular disease have a higher chance of developing unrecognized myocardial infarction, even after adjusting for multiple risk factors (48). Among other risk factors, BSA Moesteller and personal monthly income stood out.

BSA Moesteller shows a positive correlation with prediabetes, which is consistent with a study conducted in Finland in 2019 (49). In our study, as well as in the study from the Netherlands, low-income levels showed a positive correlation with prediabetes, but additional research in that direction is needed due to a lack of data on the impact of socioeconomic factors on prediabetes (50). According to a German study, low or no physical activity positively correlates with prediabetes, which was also significant in our study (44). Based on our results, we recommend increased focus by physicians in everyday clinical practice on reducing BMI and promoting increased physical activity as the main universal methods for preventing prediabetes. Furthermore, using hierarchical regression analysis, we developed predictive models of prediabetes. The final hierarchical model (model 9 in Table 4) was statistically significant with a predictive power of 27.2%. The model included 10 potential predictive factors of prediabetes, of which age and SBP were statistically the most significant. Due to a lack of similar hierarchical regression models for predicting prediabetes in the literature, we could not compare our final model. Our model has clinical implications because it shows that in the presence of multiple risk factors for prediabetes, the focus should be on age, SBP, and ACR as the main predictive factors of prediabetes, especially in individuals with visceral obesity.

Limitations and strengths of this study

Our research, like any other, has certain limitations: (i) we used only one criterion, fasting blood glucose, which may lead to an underestimation of the actual prevalence of prediabetes in the general population. However, in numerous other epidemiological studies, it was not possible to use more demanding or expensive tests, so our results can be compared with others, and the ADA states that all three methods are satisfactory for screening for prediabetes and diabetes; (ii) blood glucose measurement was done only once and not in two separate instances, but this is also the case in the majority of conducted cross-sectional epidemiological studies; (iii) this is a cross-sectional study, and therefore, we could not establish a causal relationship between observed risk factors and prediabetes, and there is a possibility of the influence of unknown risk factors.

Our research has several important and valuable strengths: (i) the prevalence of prediabetes and its association with risk factors were determined in a relatively large representative randomized sample of the general adult population of Croatia. This is the first such study conducted in Croatia and will be of great public health benefit; (ii) laboratory processing was done in one laboratory, so the possibility of inter-laboratory variability was excluded; (iii) blood glucose was determined only in participants who were fasting, as those who had eaten 12 hours before the examination were excluded, which reduces the probability of false-positive results; (iv) all anthropometric measurements were done uniformly following recent guidelines, and we also used a bioimpedance scale; (v) all demographic and clinical data were collected not only by self-reporting of participants but also by analysing medical records of family medicine physicians, so the possibility of recall bias was excluded; (vi) by using a simple, accessible, and inexpensive test, fasting blood glucose, we determined the most important predictors of prediabetes, which indicates subpopulations where it is necessary to conduct screening tests using more expensive and demanding methods, but it is also important in planning targeted education.

In conclusion, our research findings provide valuable insights into the prevalence and predictive factors of prediabetes in the Republic of Croatia. We observed an overall prevalence of 11.1%, which aligns with existing literature on the subject. Additionally, our study revealed a higher prevalence of prediabetes in men compared to women (15% vs. 9%). The identified predictive factors for prediabetes include older age, male gender, higher body weight, higher body mass index, longer waist circumference, high blood pressure, larger body surface area, a higher percentage of visceral fat percentage, decreased glomerular filtration rate, higher uric acid levels and greater albuminuria (ACR). Hypertension, smoking history, decreased physical activity, and lower personal monthly income are also associated with an increased risk of developing prediabetes. Furthermore, our final hierarchical multivariate regression model demonstrated that older age, systolic blood pressure, and albuminuria (ACR) were the most significant predictors of prediabetes, accounting for 27.2% of the predictive power. Overall, these findings emphasize the importance of early detection and intervention strategies targeting individuals with specific risk factors, such as older age, elevated blood pressure, and albuminuria (ACR), to effectively address the growing burden of prediabetes in the population. Future research and public health initiatives should consider these factors to develop targeted interventions and preventive measures to mitigate the progression of prediabetes to type 2 diabetes.

Acknowledgments

This study and prepared paper are parts of the research project of the Croatian Science Foundation, Epidemiology of hypertension and salt intake in Croatia, EH-UH 2 study (PI Bojan Jelaković). Authors would like to thank all colleagues who participated in this research project as well as to all participants.

References

1. ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 2. Classification and Diagnosis of Diabetes: *Standards of Care in Diabetes—2023*. Diabetes Care. 2023 ;46 (Supplement_1) : S19–40.
2. Echouffo-Tcheugui JB, Selvin E. Prediabetes and What It Means: The Epidemiological Evidence. Annu Rev Public Health. 2021;42(1):59–77.
3. World Health Organization, International Diabetes Federation. Definition and diagnosis of diabetes mellitus and intermediate hyperglycaemia : report of a WHO/IDF consultation. 2006 [cited 2023 Apr 3]; Available from: https://apps.who.int/iris/handle/10665/43588
4. Magliano D, Boyko EJ. IDF diabetes atlas. 10th edition scientific committee [Internet]. Brussels: International Diabetes Federation; 2021 [cited 2023 Apr 11]. Available from: https://www.diabetesatlas.org
5. Prevalence of Prediabetes Among Adults | Diabetes | CDC [Internet]. 2022 [cited 2023 Apr 4]. Available from: https://www.cdc.gov/diabetes/data/statistics-report/prevalence-of-prediabetes.html
6. Bilopavlović N, Lapić I, Rahelić D, Miškić B, Marasović Krstulović D, Pintarić H, et al. Haemoglobin A1c-based screening for prediabetes and diabetes mellitus: a multicenter study in Croatian adult population. Biochem med (Online). 2022;32(1):116–21.
7. Metelko Ž, Pavlić-Renar I, Poljičanin T, Szirovitza L, Turek S. Prevalence of diabetes mellitus in Croatia. Diabetes Research and Clinical Practice. 2008;81(2):263–7.
8. Brunetti P, Baldessin L, Pagliacci S. Prediabetes, undiagnosed diabetes and diabetes risk in Italy in 2017–2018: results from the first National screening campaign in community pharmacies. Journal of Public Health. 2022;44(3):499–506.
9. Brož J, Malinovská J, Nunes MA, Kučera K, Rožeková K, Žejglicová K, et al. Prevalence of diabetes and prediabetes and its risk factors in adults aged 25–64 in the Czech Republic: A cross-sectional study. Diabetes Research and Clinical Practice. 2020;170:108470.
10. Mokáň M, Galajda P, Prídavková D, Tomášková V, Šutarík Ľ, Kručinská Ľ, et al. Prevalence of diabetes mellitus and metabolic syndrome in Slovakia. Diabetes Research and Clinical Practice. 2008 ;81(2):238–42.
11. Lailler G, Piffaretti C, Fuentes S, Nabe HD, Oleko A, Cosson E, et al. Prevalence of prediabetes and undiagnosed type 2 diabetes in France: Results from the national survey ESTEBAN, 2014–2016. Diabetes Research and Clinical Practice. 2020;165:108252.
12. Eades CE, France EF, Evans JMM. Prevalence of impaired glucose regulation in Europe: a meta-analysis. Eur J Public Health. 2016;26(4):699–706.
13. Tabák AG, Jokela M, Akbaraly TN, Brunner EJ, Kivimäki M, Witte DR. Trajectories of glycaemia, insulin sensitivity, and insulin secretion before diagnosis of type 2 diabetes: an analysis from the Whitehall II study. The Lancet. 2009;373(9682):2215–21.
14. Abdul-Ghani MA, Tripathy D, DeFronzo RA. Contributions of β-Cell Dysfunction and Insulin Resistance to the Pathogenesis of Impaired Glucose Tolerance and Impaired Fasting Glucose. Diabetes Care. 2006;29(5):1130–9.
15. Weir GC, Bonner-Weir S. Five Stages of Evolving Beta-Cell Dysfunction During Progression to Diabetes. Diabetes. 2004;53(suppl_3):S16–21.
16. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA. Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. Diabetologia. 2004;47(1):31–9.
17. Dagogo-Jack S. Diabetes risks from prescription & non-prescription drugs: mechanisms and approaches to risk reduction. Alexandria, Virginia: American Diabetes Association; 2016. 133 p.
18. Kim JY, Nasr A, Tfayli H, Bacha F, Michaliszyn SF, Arslanian S. Increased Lipolysis, Diminished Adipose Tissue Insulin Sensitivity, and Impaired β-Cell Function Relative to Adipose Tissue Insulin Sensitivity in Obese Youth With Impaired Glucose Tolerance. Diabetes. 2017;66(12):3085–90.
19. Toft-Nielsen MB, Damholt MB, Madsbad S, Hilsted LM, Hughes TE, Michelsen BK, et al. Determinants of the Impaired Secretion of Glucagon-Like Peptide-1 in Type 2 Diabetic Patients. The Journal of Clinical Endocrinology & Metabolism. 2001;86(8):3717–23.
20. Gerstein HC, Santaguida P, Raina P, Morrison KM, Balion C, Hunt D, et al. Annual incidence and relative risk of diabetes in people with various categories of dysglycemia: A systematic overview and meta-analysis of prospective studies. Diabetes Research and Clinical Practice. 2007;78(3):305–12.
21. Shaw JE, Zimmet PZ, de Courten M, Dowse GK, Chitson P, Gareeboo H, et al. Impaired fasting glucose or impaired glucose tolerance. What best predicts future diabetes in Mauritius? Diabetes Care. 1999;22(3):399–402.
22. Gabir MM, Hanson RL, Dabelea D, Imperatore G, Roumain J, Bennett PH, et al. The 1997 American Diabetes Association and 1999 World Health Organization criteria for hyperglycemia in the diagnosis and prediction of diabetes. Diabetes Care. 2000;23(8):1108–12.
23. Bennasar-Veny M, Fresneda S, López-González A, Busquets-Cortés C, Aguiló A, Yañez AM. Lifestyle and Progression to Type 2 Diabetes in a Cohort of Workers with Prediabetes. Nutrients. 2020 ;12(5):1538.

24. Richter B, Hemmingsen B, Metzendorf MI, Takwoingi Y. Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia. Cochrane Metabolic and Endocrine Disorders Group, editor. Cochrane Database of Systematic Reviews [Internet]. 2018 Oct 29 [cited 2023 Apr 15];2018(11). Available from: http://doi.wiley.com/10.1002/14651858.CD012661.pub2
25. Schmitt VH, Leuschner A, Jünger C, Pinto A, Hahad O, Schulz A, et al. Cardiovascular profiling in the diabetic continuum: results from the population-based Gutenberg Health Study. Clin Res Cardiol. 2022;111(3):272–83.
26. Ali MK, Bullard KM, Saydah S, Imperatore G, Gregg EW. Cardiovascular and renal burdens of prediabetes in the USA: analysis of data from serial cross-sectional surveys, 1988–2014. The Lancet Diabetes & Endocrinology. 2018;6(5):392–403.
27. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care. 1999;22(2):233–40.
28. Wang J, Liu L, Zhou Y, Wang C, Hu H, Hoff K, et al. Increased fasting glucose and the prevalence of arterial stiffness: a cross-sectional study in Chinese adults. Neurological Research. 2014;36(5):427–33.
29. Huang Y, Cai X, Mai W, Li M, Hu Y. Association between prediabetes and risk of cardiovascular disease and all cause mortality: systematic review and meta-analysis. BMJ. 2016 Nov 23;i5953.
30. Saydah SH, Loria CM, Eberhardt MS, Brancati FL. Subclinical States of Glucose Intolerance and Risk of Death in the U.S. Diabetes Care. 2001;24(3):447–53.
31. Barr ELM, Zimmet PZ, Welborn TA, Jolley D, Magliano DJ, Dunstan DW, et al. Risk of Cardiovascular and All-Cause Mortality in Individuals With Diabetes Mellitus, Impaired Fasting Glucose, and Impaired Glucose Tolerance: The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation. 2007;116(2):151–7.
32. Echouffo-Tcheugui JB, Narayan KM, Weisman D, Golden SH, Jaar BG. Association between prediabetes and risk of chronic kidney disease: a systematic review and meta-analysis. Diabet Med. 2016;33(12):1615–24.
33. Plantinga LC, Crews DC, Coresh J, Miller ER, Saran R, Yee J, et al. Prevalence of Chronic Kidney Disease in US Adults with Undiagnosed Diabetes or Prediabetes. Clinical Journal of the American Society of Nephrology. 2010;5(4):673–82.
34. Bahar A, Makhlough A, Yousefi A, Kashi Z, Abediankenari S. Correlation Between Prediabetes Conditions and Microalbuminuria. Nephro Urol Mon. 2013;5(2):741–4.
35. Lee CC, Perkins BA, Kayaniyil S, Harris SB, Retnakaran R, Gerstein HC, et al. Peripheral Neuropathy and Nerve Dysfunction in Individuals at High Risk for Type 2 Diabetes: The PROMISE Cohort. Diabetes Care. 2015;38(5):793–800.
36. Kirthi V, Perumbalath A, Brown E, Nevitt S, Petropoulos IN, Burgess J, et al. Prevalence of peripheral neuropathy in pre-diabetes: a systematic review. BMJ Open Diabetes Research and Care. 2021;9(1):e002040.
37. Jin M, Yuan S, Wang B, Yi L, Wang C. Association Between Prediabetes and Erectile Dysfunction: A Meta-Analysis. Front Endocrinol. 2022;12:733434.
38. Huang Y, Cai X, Qiu M, Chen P, Tang H, Hu Y, et al. Prediabetes and the risk of cancer: a meta-analysis. Diabetologia. 2014;57(11):2261–9.
39. CDC. Prediabetes - Your Chance to Prevent Type 2 Diabetes [Internet]. Centers for Disease Control and Prevention. 2021 [cited 2023 Apr 18]. Available from: https://www.cdc.gov/diabetes/basics/prediabetes.html
40. Hashemi SJ, Karandish M, Cheraghian B, Azhdari M. Prevalence of prediabetes and associated factors in southwest iran: results from Hoveyzeh cohort study. BMC Endocr Disord. 2022;22(1):72.
41. Brannick B, Dagogo-Jack S. Prediabetes and Cardiovascular Disease. Endocrinology and Metabolism Clinics of North America. 2018;47(1):33–50.
42. Croatia diabetes report 2000 — 2045 [Internet]. [cited 2023 Apr 25]. Available from: https://diabetesatlas.org/data/
43. Jermendy G, Nádas J, Szigethy E, Széles G, Nagy A, Hídvégi T, et al. Prevalence Rate of Diabetes Mellitus and Impaired Fasting Glycemia in Hungary: Cross-Sectional Study on Nationally Representative Sample of People Aged 20-69 Years. Croat Med J. 2010;51(2):151–6.
44. Greiner GG, Emmert-Fees KMF, Becker J, Rathmann W, Thorand B, Peters A, et al. Toward targeted prevention: risk factors for prediabetes defined by impaired fasting glucose, impaired glucose tolerance and increased HbA1c in the population-based KORA study from Germany. Acta Diabetol. 2020 ; 57(12):1481–91.
45. Mota M, Popa SG, Mota E, Mitrea A, Catrinoiu D, Cheta DM, et al. Prevalence of diabetes mellitus and prediabetes in the adult Romanian population: PREDATORR study. Journal of Diabetes. 2016;8(3):336–44.
46. Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: the Di@bet.es Study. Diabetologia. 2012 ;55(1):88–93.

47. Budiastutik I, Kartasurya MI, Subagio HW, Widjanarko B. High Prevalence of Prediabetes and Associated Risk Factors in Urban Areas of Pontianak, Indonesia: A Cross-Sectional Study. Choubey M, editor. Journal of Obesity. 2022;2022:1–9.
48. Brandon Stacey R, Leaverton PE, Schocken DD, Peregoy JA, Bertoni AG. Prediabetes and the association with unrecognized myocardial infarction in the multi-ethnic study of atherosclerosis. American Heart Journal. 2015;170(5):923–8.
49. Palmu S, Rehunen S, Kautiainen H, Eriksson JG, Korhonen PE. Body surface area and glucose tolerance – The smaller the person, the greater the 2-hour plasma glucose. Diabetes Research and Clinical Practice. 2019;157:107877.
50. Qi Y, Koster A, Van Boxtel M, Köhler S, Schram M, Schaper N, et al. Adulthood Socioeconomic Position and Type 2 Diabetes Mellitus—A Comparison of Education, Occupation, Income, and Material Deprivation: The Maastricht Study. IJERPH. 2019;16(8):1435.

Conflict of Interest

None.

Supplementary Materials

Table 1S. Clinical characteristics of participants categorized by sex[a]

	Whole group	Men	Women	p-value
%, (n)	100 (687)	33,9 (233)	66,1 (454)	-
(S) Glucose (mmol/L)	4,7 (4,3 – 5,2)	4,8 (4,4 – 5,4)	4,6 (4,2 – 5,1)	< 0,001
(S) Glucose categories				
Individuals with normal glucose levels	85,6 (588)	78,1 (182)	89,4 (406)	< 0,001
Prediabetics	11,1 (76)	15 (35)	9 (41)	
Untreated individuals with diabetes	3,4 (23)	6,9 (16)	1,5 (7)	
Age (years)	56,15 ± 14,51	56,75 ± 14,4	55,84 ± 14,57	0,719
Height (cm)	166,72 ± 9,44	175,28 ± 7,38	162,29 ± 7,03	< 0,001
Weight (kg)	80,04 ± 16,9	90,09 ± 16,46	74,87 ± 14,65	< 0,001
BMI (kg/m^2)	28,61 ± 5,07	29,09 ± 4,3	28,37 ± 5,41	0,036
BMI <25, % (n)	25,3 (168)	16,4 (37)	30 (131)	
BMI 25-30, % (n)	37,7 (250)	42,5 (96)	35,2 (154)	< 0,001
BMI ≥30, % (n)	37 (245)	41,2 (93)	34,8 (152)	
BSA Moesteller (m^2)	1,91 ± 0,22	2,08 ± 0,18	1,83 ± 0,19	< 0,001
Waist circumference (cm)	95,53 ± 14,35	101,92 ± 12,03	92,3 ± 14,37	< 0,001
Body fat (%)	36,35 ± 9,67	28,18 ± 6,97	40,20 ± 8,28	< 0,001
Muscle mass (%)	26,6 (23,7 – 30,85)	32,1 (30 – 34,95)	24,9 (22,73 – 27,3)	< 0,001
BMR (kkcal)	1587,32 ± 245,96	1813,53 ± 198,3	1480,68 ± 187,14	< 0,001
Visceral fat (%)	10,86 ± 4,61	14,16 ± 4,96	9,31 ± 3,49	< 0,001
SBP (mmHg)	133,17 ± 17,99	137,79 ± 17,26	130,82 ± 17,92	< 0,001
DBP (mmHg)	82,83 ± 10,15	85,89 ± 10,56	81,28 ± 9,58	< 0,001
Duration of hypertension (years)	9 (4 – 15)	9 (4 – 14)	10 (4 – 15)	0,266
HR (bpm)	73,70 ± 11,09	72,65 ± 11,85	74,24 ± 10,65	0,148
PY	12 (5,25 – 30)	20 (7,25 – 38,25)	10,4 (5 – 22,5)	< 0,001
AH				
Yes, % (n)	50,5 (345)	49,6 (115)	51 (230)	0,113
No, % (n)	48,2 (329)	47,9 (111)	48,3 (218)	
Don't know, % (n)	1,3 (9)	2,6 (6)	0,7 (3)	
CKD				
Yes, % (n)	2,9 (20)	4,7 (11)	2 (9)	0,102
No, % (n)	93,3 (637)	92,2 (214)	93,8 (423)	
Don't know, % (n)	3,8 (26)	3 (7)	4,2 (19)	

Table 1S. Clinical characteristics of participants categorized by sex - continued

Smoking status				
Never, % (n)	55,9 (384)	46,4 (108)	60,8 (276)	0,797
Ex smoker, % (n)	16,9 (116)	27 (63)	11,7 (53)	
Smoker, % (n)	27,2 (187)	26,6 (62)	27,5 (125)	
Exercise intensity				
Low, % (n)	46,3 (318)	41,2 (96)	48,9 (222)	
Medium, % (n)	33,8 (232)	42,9 (100)	29,1 (132)	0,001
High, % (n)	0 (0)	0 (0)	0 (0)	
Don't know, % (n)	19,9 (137)	15,9 (37)	22 (100)	

[a]Continuous variables are expressed as mean ± SD for normally distributed variables and as median and interquartile range for non-normally distributed variables. Categorical variables are expressed as percentages (number). BMI: body mass index; BSA: body surface area; SBP: systolic arterial pressure; BMR: basal metabolic rate; SBP: diastolic arterial pressure; HR: heart rate; bpm: beats per minute PY: pack-years; AH: arterial hypertension; CKD: chronic kidney disease

Table 2S. Laboratory characteristics of participants classified by sex[a]

	Whole group	Men	Women	p-value
Serum creatinine (mmol/L)	71 (63 – 82)	83 (76 – 91)	66 (60 – 74)	< 0,001
CKD Epi (ml/min/1,73 m^2)	88,43 ± 18,36	88,02 ± 18,03	88,64 ± 18,55	0,871
CKD Mi (ml/min/1,73 m^2)	97,74 ± 23,34	105,84 ± 24,56	93,48 ± 21,52	< 0,001
Serum urate (mmol/L)	290,01 ± 79,7	338,99 ± 72,76	264,81 ± 70,97	< 0,001
Total cholesterol (mmol/L)	5,31 ± 1,12	5,24 ± 1,2	5,35 ± 1,08	0,172
Triglycerides (mmol/L)	1,2 (0,88 – 1,68)	1,27 (0,93 – 1,83)	1,17 (0,87 – 1,6)	0,004
HDL cholesterol (mmol/L)	1,48 ± 0,39	1,33 ± 0,39	1,55 ± 0,37	< 0,001
LDL cholesterol (mmol/L)	3,22 ± 1,02	3,20 ± 1,06	3,24 ± 1	0,506
Sodium/potassium ratio	3,35 ± 1,35	3,62 ± 1,49	3,22 ± 1,25	0,002
Daily salt intake (grams)	9,8 ± 4,71	11,37 ± 5,18	8,98 ± 4,23	< 0,001
ACR	16,69 (7,3 – 39,64)	14,5 (6,02 – 35,4)	18,17 (8,11 – 38,82)	0,018

[a]Values of continuous variables are expressed as mean ± SD in case of normally distributed variables, and as median and interquartile range in case of non-normally distributed variables. CKD EPI: Chronic kidney disease epidemiology collaboration; CKD Mi: CKD-EPI equation adjusted for individual body surface area values calculated using the Mosteller equation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ACR: albumin-to-creatinine ratio

Table 3S. Statistically non-significant results of Spearman's correlation between predictor variables and prediabetes status (p > 0.05)[a]

Independent variable	Correlation coefficient	p-value	95% CI
Education	-0,038	0,324	-0,116 – 0,040
Professional qualification	-0,058	0,138	-0,135 – 0,021
Duration of hypertension	0,044	0,428	-0,068 – 0,155
Height (cm)	0,006	0,878	-0,073 – 0,085
HR (bpm)	0,031	0,436	-0,049 – 0,110
Body fat (%)	0,034	0,446	-0,056 – 0,124
Muscle mass (%)	-0,017	0,700	-0,108 – 0,073
CKD Mi (ml/min)	-0,051	0,221	-0,135 – 0,033
Total cholesterol (mmol/L)	0,000	0,996	-0,079 – 0,078
HDL cholesterol (mmol/L)	-0,036	0,355	-0,114 – 0,042
LDL cholesterol (mmol/L)	-0,009	0,813	-0,087 – 0,069
Sodium/potassium ratio	-0,076	0,054	-0,154 – (-0,004)
Daily salt intake (grams)	-0,015	0,697	-0,095 – 0,064

[a]HR: heart rate; bpm: beats per minute; CKD Mi: CKD EPI equation: adjusted for individual body surface area values calculated using the Moesteller equation; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Table 4S. Statistically non-significant results of univariate binary logistic regression analysis[a]

	ß	p-value	OR	95% CI
Duration of hypertension (years)	0,011	0,499	1,011	0,979 – 1,044
Height (cm)	0,003	0,816	1,003	0,978 – 1,029
HR (bpm)	0,010	0,373	1,010	0,988 – 1,032
Body fat (%)	0,011	0,430	1,011	0,984 – 1,039
Muscle mass (%)	-0,014	0,547	0,986	0,944 – 1,031
CKD Mi (ml/min)	-0,009	0,139	0,991	0,98 – 1,003
Total cholesterol (mmol/L)	0,063	0,562	1,065	0,861 – 1,318
Triglycerides (mmol/L)	0,165	0,183	1,180	0,925 – 1,504
HDL cholesterol (mmol/L)	-0,245	0,450	0,782	0,414 – 1,479
LDL cholesterol (mmol/L)	0,060	0,617	1,061	0,841 – 1,340
Sodium/potassium ratio	-0,136	0,169	0,873	0,72 – 1,059
Daily salt intake (grams)	-0,012	0,665	0,988	0,938 – 1,042
Average familiy monthly income	-0,336	0,168	0,714	0,433 – 1,153
Education	-0,366	0,172	0,693	0,410 – 1,173
Professional qualification	-0,152	0,596	0,859	0,491 – 1,504
CKD	0,803	0,167	2,233	0,715 – 6,972
Smoking status	-0,229	0,422	0,796	0,455 – 1,391

[a]Average family monthly income: <5000 vs. >5000; Education: <8 years vs. >8 years; Professional qualification: low and intermediate vs. high (high school, bachelor's, and master's degrees); CKD: yes vs. no; Smoking status: yes vs. no
HR: heart rate; bpm: beats per minute; CKD Mi: CKD EPI equation adapted for individual body surface area values calculated using Moesteller equation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CKD: chronic kidney disease

Analysis of improving business processes by implementing the lean concept at the level of tertiary healthcare

Edin Medjedovic[1], Sabina Sehic Krslak[2], Milan Stanojević[3,4], Zlatan Zvizdic[5], Edin Begic[6], Jasmin Nurkovic[7], Anis Cerovac[8], Alma Suljevic[9], Adnan Kulo[10]

[1] Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina, Department of Gynecology, Obstetrics and Reproductive Medicine, Sarajevo Medical School, School of Science and Technology, Sarajevo, Bosnia and Herzegovina
[2] Faculty of Management and Business Economics, University of Travnik
[3] Neonatal Unit, Department of Obstetrics and Gynecology, Medical School University of Zagreb, Zagreb, Croatia
[4] Department of Obstetrics and Gynecology, University Hospital "Sveti Duh", Zagreb, Croatia,
[5] Clinic for Children's Surgery, Clinical Center of the University of Sarajevo, Bosnia and Herzegovina
[6] Department of Cardiology, General Hospital "Prim.dr Abdulah Nakaš", Sarajevo, Bosnia and Herzegovina, Department of Pharmacology, Sarajevo Medical School, Sarajevo School of Science and Technology, Sarajevo, Bosnia and Herzegovina
[7] Center for Regeneration and Rehabilation, Novi Pazar, Serbia
[8] Department of Gynecology and obstetrics and Department of Anatomy, General Hospital Tešanj and University of Tuzla,
[9] Clinic of Gynecology and Obstetrics, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina
[10] Clinic for abdominal surgery, Clinical Center University of Sarajevo, Sarajevo, Bosnia and Herzegovina, Sarajevo Medical School, School of Science and Technology, Sarajevo, Bosnia and Herzegovina

OPEN ACCESS

Correspondence:
Sabina Sehic - Krslak
sabina.sehic.krslak@gmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 02 December 2022
Accepted: 15 January 2023
Published: 26 June 2023

Citation:
Medjedovic E, Sehic Krslak S, Stanojević M, Zvizdic Z, Begic E, Nurkovic J, Cerovac A, Suljevic A, Kulo A. Analysis of improving business processes by implementing the lean concept at the level of tertiary healthcare 556=62-63 (2023): 34-42
DOI: 10.21857/9e31lh65vm

Abstract:

Introduction. The success of healthcare organizations depends on the quality and speed of providing services to patients. Synonym for the term success of health care organization is the implementation of modern concepts Synonymous with the success of healthcare organizations is the implementation of modern concepts. In this paper, the emphasis is on the *lean* concept, affects the quality and speed of providing health services.

Subject of research. The subject being researched in this paper is a *lean* concept which essence is determined by the implementation of methods that affect the speed and quality of providing health services. The aim of the work is to point out the actuality of the *lean* concept and its application at the tertiary level of health care. Examine the opinion of healthcare workers about the effects that would be achieved by applying the new management system (*lean* concept).

Aim of this paper is to indicate the actuality of the *lean* concept and its application at the tertiary level of health care system. Examine the opinion of healthcare workers about the effects that would be achieved by applying the new management system (*lean* concept). More precise possibilities of implementing the *lean* methodology, which can be used to improve clinical processes.

Materials and methods. The research was conducted by designing and using research questionnaires. Questionnaire structured by the author for the purposes of research in this paper. The questionnaire was sent to 472 employees' mail addresses and was filled out by 91 employees. One of the reasons for the lower questionnaire return rate is the lack of familiarity of employees with the *lean* concept and its effects on the provision of health services. The return rate of referrals indicates the need for prior presentation and familiarization with the concept itself and its impact on business processes. A Likert scale was used to assess the opinions of healthcare services workers about the effects that would be achieved by applying the *lean* concept at the tertiary level. Medical wastes are shown in the oncology department (case analysis). We statistically processed the data obtained from the questionnaire using

the SPSS 20.0 software package. The results are presented tabularly and graphically. The following methods are used in the paper: analysis method, inductive - deductive method, synthesis method, description method and proof method.
Results. The results of the research showed that (analysis of health organizations that apply the *lean* concept) and the opinion of health workers about the possibility of applying the *lean* concept at the tertiary level of health care has a positive impact on improving the efficiency of the provision of health services. The interpretation of the correlation coefficient from the previous table indicates the existence of a positive relationship between the effectiveness and efficiency of business processes (r=0.846; p<0,05).
Based on the literature review and the obtained results, it was determined that there is no formalized concept with instructions on the implementation of clinical process improvement methods. There was a positive impact on improving the efficiency of the provision of health services, through the implementation of modern methods. The review of the literature and the obtained results revealed that there is no formalized concept with instructions on the implementation of clinical process improvement methods.
Conclusion The expected positive effects of the implementation of the lean concept at the tertiary level of the health care of are manifested through: faster service delivery to patients, reduction of service waiting time and general improvement of business processes. The implementation of the *lean* concept would reduce medical waste, which would positively affect the quality of health care services.

Keywords: methods, health care services, clinical processes.

Sažetak:

Analiza unapređenja poslovnih procesa implementacijom lean koncepta na razini tercijarne zdravstvene zaštite
Uvod. Uspjeh zdravstvenih organizacija ovisi o kvaliteti i brzini pružanja usluga pacijentima. Sinonim za pojam uspjeh zdravstvene organizacije je implementacija modernih koncepata Sinonim za uspjeh zdravstvene organizacije je implementacija modernih koncepata. U ovom radu naglasak je na lean konceptu koji utječe na kvalitetu i brzinu pružanja zdravstvenih usluga.
Predmet istraživanja. Predmet istraživanja u ovom radu je lean koncept čija je bit određena primjenom metoda koje utječu na brzinu i kvalitetu pružanja zdravstvenih usluga. Cilj rada je ukazati na aktualnost lean koncepta i njegovu primjenu na tercijarnoj razini zdravstvene zaštite. Ispitati mišljenje zdravstvenih radnika o učincima koji bi se postigli primjenom novog sustava upravljanja (lean koncept).
Cilj ovog rada je ukazati na aktualnost lean koncepta i njegovu primjenu na tercijarnoj razini zdravstvenog sustava. Ispitati mišljenje zdravstvenih radnika o učincima koji bi se postigli primjenom novog sustava upravljanja (lean koncept). Preciznije mogućnosti implementacije lean metodologije, koja se može koristiti za poboljšanje kliničkih procesa.
Materijali i metode. Istraživanje je provedeno osmišljavanjem i korištenjem istraživačkih upitnika. Upitnik koji je autor strukturirao za potrebe istraživanja u ovom radu. Upitnik je poslan na mail adrese 472 zaposlenika, a ispunio ga je 91 zaposlenik. Jedan od razloga niže stope vraćanja upitnika je neupoznatost zaposlenika s lean konceptom i njegovim učincima na pružanje zdravstvenih usluga. Stopa povrata preporuka ukazuje na potrebu prethodnog predstavljanja i upoznavanja sa samim konceptom i njegovim utjecajem na poslovne procese. Likertovom ljestvicom ocijenjeno je mišljenje zdravstvenih djelatnika o učincima koji bi se postigli primjenom lean koncepta na tercijarnoj razini. Medicinski otpad prikazan je na onkološkom odjelu (analiza slučaja). Podatke dobivene iz upitnika statistički smo obradili pomoću programskog paketa SPSS 20.0. Rezultati su prikazani tablično i grafički. U radu se koriste sljedeće metode: metoda analize, induktivno-deduktivna metoda, metoda sinteze, metoda deskripcije i metoda dokaza.
Rezultati. Rezultati istraživanja pokazali su da (analiza zdravstvenih organizacija koje primjenjuju lean koncept) i mišljenje zdravstvenih radnika o mogućnosti primjene lean koncepta na tercijarnoj razini zdravstvene zaštite pozitivno utječe na poboljšanje učinkovitosti pružanja usluga. zdravstvenih usluga.

Interpretacija koeficijenta korelacije iz prethodne tablice ukazuje na postojanje pozitivnog odnosa između efektivnosti i učinkovitosti poslovnih procesa (r=0,846; p<0,05).
Na temelju pregleda literature i dobivenih rezultata utvrđeno je da ne postoji formalizirani koncept s uputama o primjeni metoda poboljšanja kliničkog procesa. Ostvaren je pozitivan utjecaj na poboljšanje učinkovitosti pružanja zdravstvenih usluga, kroz primjenu suvremenih metoda. Pregledom literature i dobivenih rezultata utvrđeno je da ne postoji formalizirani koncept s uputama o primjeni metoda poboljšanja kliničkog procesa.
Zaključak Očekivani pozitivni učinci implementacije lean koncepta na tercijarnoj razini zdravstvene zaštite očituju se kroz: bržu isporuku usluga pacijentima, smanjenje vremena čekanja na uslugu i opće poboljšanje poslovnih procesa. Primjenom lean koncepta smanjio bi se medicinski otpad, što bi pozitivno utjecalo na kvalitetu zdravstvenih usluga.

Ključne riječi: metode, zdravstvene usluge, klinički procesi.

Introduction

The *lean* concept is a system of leadership, management and organization of the work process, with a focus on eliminating all types of waste (resources, time, energy). The expected effect of the implementation of the *lean* concept is to reduce business costs, through the elimination of wastage. The topic of implementation of modern models at the level of tertiary health care is particularly topical. Khamidullina and Puryaev [1, 2], claim that companies that are world leaders in their industries actively apply the *lean* concept. It first appeared in production. Production and health care differ in many ways, but there are also similarities that enable the application of *lean* principles when providing health services. For the *lean* concept (suppliers, inputs, process, outputs, customers) has found application in the management of various organizations [3, 4], and the challenge is to apply it. The increase in the need for faster, cheaper and better quality services in the health sector, and in conditions of limited resources, puts before tertiary health care the necessity of searching for and applying new models and tools aimed at improving the functioning of the system. Therefore, we believe that the given research area has justification and represents a challenge for researchers.
Despite the successful implementation of the *lean* concept, many obstacles have also appeared in its application. Elkhairi et al. refer to research by the authors Bajjou and Chafi from 2018, emphasizing that they classified these barriers into three different categories: economic, managerial, and technical and social barriers. Managerial and technical barriers are lack of planning, lack of expertise, lack of top management commitment, lack of strategic perspective, lack of understanding of lean production. The economic barrier is limited resources. A social barrier is resistance to change.

Materials and methods

During the preparation of the paper, data were collected from the latest relevant scientific articles and books, and health systems that applied modern concepts of optimization of clinical processes were analyzed. The methods used in this work belongs to analytical and synthetic group of methods. The analysis method was used for the purpose of analyzing the available literature that deals with the given subject of research, and for the purpose of analyzing the obtained research results. The inductive method was used as a logical reasoning procedure, based on the analysis of research problems and research results. The deductive method was used when making conclusions about whether the goal of the research was achieved and making general conclusions reached during the research. The method of synthesis was used in order to connect all elements into an integral whole and reach the general conclusion of the work.

Review of earlier research

In the review of previous studies, we will describe the most important research within the Lean methodology. We believe this to be important, as SIPOC is merely one of the methods within the *lean* methodology. Another reason is that, through *lean* methodology and its effects, it is possible to clearly point out the necessity of implementing contemporary models in healthcare organizations.
A study by Dickson et al. [5], on the implementation of the *lean* methodology at the emergency departments of four public hospitals in Massachusetts, Worchester, Orlando, and Iowa City, showed that, with the help of the *lean* methodology, the patients' waiting time was reduced. The decreased waiting time directly affected the increase in the satisfaction of the patients.
A study by Zoe Radnor [6] showed that the implementation of this methodology at the Scotland Cancer Treatment Center resulted in a reduction of the time patients waited for examinations, as well as in the improvement of patient flow through the system of service provision by 48%. Based on the review of the literature dealing with the research topic of the present study, a research hypothesis was formulated: The application *lean* concept can positively affect the efficiency of the clinical process.

Opportunities for implementing of the lean concept in healthcare

There are many challenges which healthcare institutions face when implementing *lean* concept. There are many unclear issues when it comes to determining values in healthcare. The greatest challenge of implementing contemporary *lean* concept in healthcare is finding a way to improve service for patients. The expected improvements resulting from the implementation of the *lean* concept are intended for: patients, healthcare workers, healthcare institutions.

For patients [7]:
- Decrease in the time spent in hospital
- Increase in satisfaction
- Decrease in waiting time
- Improvement of service quality
- Decrease in the number of errors
- Improvement of information flow

For healthcare workers [8]:
- Elimination of waste
- Decrease of overtime
- Decrease of the workload
- Increase in satisfaction
- A more peaceful and better organized work environment

For healthcare institutions [9]:
- Decrease in equipment
- Increase in the number of examined patients
- Decrease in costs
- Improvement of information flow

Results

Table 1: Structure of respondents

Position	Number	Procesnt (%)
Medical doctors – specialists	23	25
Doctors specializing	5	5,4
Senior nurses	24	26,4
Nurse	27	30
Administrative staff	10	11
Other	2	2,2
Total	91	**100**

Source. Author's research

Table 2: Respondents' opinions about the effects that would be achieved by applying the lean concept at the tertiary level of healthcare services

VARIJABLES	SIGNIFICANCE				
	1 Strongly Disapprove	2 Dispprove	3 Undecided	4 Approve	5 Strongly Approve
Effectiveness of business processes	0,0	3,4	13,0	43,0	46,0
Process efficiency	0,5	2,4	4,3	32,9	59,9
Process flexibility	0,5	5,8	22,7	39,1	31,9
Output quality	0,0	1,0	7,2	38,2	53,6
Duration of the process	0,0	4,3	17,9	42,0	35,7
Potential cost savings	2,4	10,6	40,1	35,7	18,8
Frequency of process execution	5,3	19,3	29,5	26,1	19,8
Degree of process documentation	3,9	11,6	18,4	40,1	26,1
Degree of process performance monitoring	0,0	1,0	11,1	49,8	38,2
Continuous monitoring of activities that do not create added value	0,5	4,3	23,7	48,8	22,7
The output from the process is intended for patients	4,3	10,1	20,3	30,4	34,8

Source. Author's research

Table number 2 presents the results of a survey of the attitudes of healthcare workers as they see the effects of the implementation of the lean concept at the level of tertiary healthcare. From the results, it can be seen that in over 80% of cases, the following were rated as significant or very significant:
1. Process efficiency,
2. Process effectiveness,
3. Process output quality,
4. Continuous monitoring of activities that do not create value.
This result confirms the existence of a basis for the implementation of the *lean* concept. One of the fundamental principles of the *lean* concept is the monitoring of activities that do not create value, there before the healthcare system needs effective and efficient processes, which healthcare workers have marked as a priority. Effective and efficient processes should each result in the quality of the process output, which was assessed as a significant priority in the research. Accordingly, a correlation test of the effectiveness and efficiency of business processes was performed.

Table 3: Correlation of effectiveness and efficiency of business processes

Correlations			
Varijabla		Effectiveness of business processes	Efficiency of business processes
Effectiveness of business processes	Pearson Correlation	1	.846*
	Sig. (2-tailed)		.016
	N	7	7
Efficiency of business processes	Pearson Correlation	.846*	1
	Sig. (2-tailed)	.016	
	N	7	7

*. Correlation is significant at the 0.05 level (2-tailed).

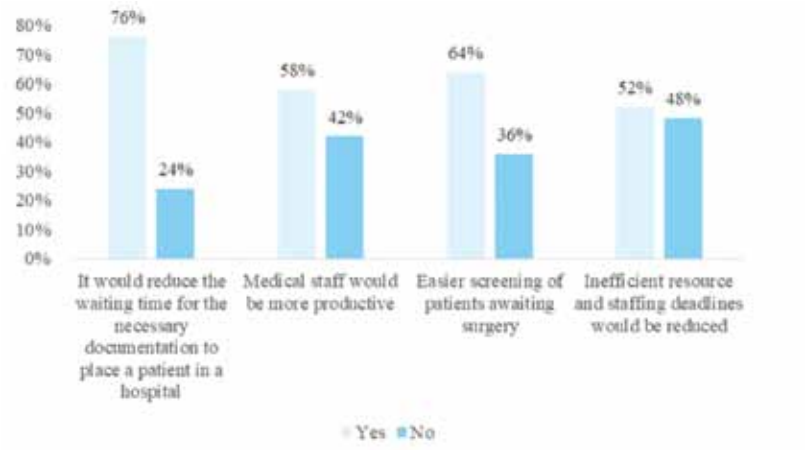
Source. Author's research

The interpretation of the correlation coefficient from the previous table indicates the existence of a positive relationship between the effectiveness and efficiency of business processes. (r=0.846; p<0,05). The results in the table (*Correlation of effectiveness and efficiency*) confirm the conclusion that there is a significant positive relationship between the variable effectiveness of business processes and the efficiency of business processes. Greater effectiveness of business processes contributes to the efficiency of business processes. Assessment of the efficiency of business processes at the level of tertiary health care is carried out through:

1. Patient satisfaction;
2. Quicker checking of the waiting list of patients;
3. Decreasing the waiting time for placing patients in the hospital;
4. More efficient performance of activities within the process.
5. Reducing administrative costs and losses.

On the other hand, the criteria that in more than 20% of cases are marked as not significant or slightly significant are: the degree to which the process is documented, the scope of the process, the number of employees involved in the execution of the process, who is affected by the process change and whether it is necessary little effort to achieve improvements quickly. This research result shows who is involved in the process itself is less important. Therefore, healthcare professionals see the purpose of a process in quality implementation.

Graph 1: The attitudes and opinions of healthcare workers at the tertiary level about the expected effects of the implementation of the lean concept



Source. Author's research

Based on the previous graph (*graph1*), you can see an overview of the results of respondents' statements about the effects that would be achieved by implementing the *lean* concept. The highest redundancy rate agreement is regarding the reduction of the waiting time for the necessary documentation for the placement of patients in the hospital. It is also one of the fundamental principles of the *lean* concept - the satisfaction of end users, in this case patients. The second-ranked effect according to the respondents is a simpler check on the waiting list of patients for surgical procedures. The lowest degree of agreement among respondents is with the statement to reduce the inefficient flow of resources and employees.

Table 4 Example of waste at the tertiary level of healthcare Department of Oncology

Type of wastage	Mislabeled tubes	Oncology patient care
Defects	You took the tubes with the blood sample unused	Inadequate therapy for the patient
Excess production	Moving test tubes from the place of sample collection to testing	Waiting for chemotherapy
Transport	Waiting for the sample to be tested	Spatial distance of the accommodated patient to the place of chemotherapy
Waiting	Test reagents have expired	Expired dates for chemotherapy drugs
Supplies	Too many reagents	Patients wait for doctors due to delays that exceed capacity
Motion	Time to print labels that are not in use	Nurses in search of poorly located deliveries
Redundant processing	Repeating the entire examination due to one bad result	Time spent creating a schedule that is not followed.
Human potentials	Employees' ideas are not listened to	

Source. Author's research

Discusion

Health care systems in Bosnia and Herzegovina (BH) are focused on traditional business process improvement systems. They are more precisely focused on business processes that add value. The *lean* concept also focuses on processes that do not add value [11]. The basic principle of the lean concept is to learn to see waste. The first observed medical wastages were in Dutch and British hospitals [12,13]. In our research, we have shown the results of wastage at the tertiary level of health care - the Department of Oncology (table 4). By comparing the research, it was observed the difference in the ranking of the type of wastage according to priorities and according to the frequency of occurrence. Based on the comparison of the results, it can be concluded that the emphasis in Dutch and British hospitals is on improving efficiency (speed of service delivery), while BH health institutions, the emphasis is more on effectiveness, i.e. on the mode of operation (reduction of defects). The aforementioned results confirm the necessity of improving the efficiency of providing health services in Bosnia and Herzegovina. As the correction of defects is related to the human factor, in our research we went a step further compared to research and analyzed human potential, as one of the causes of possible wastage. The obtained results indicate that not listening to the ideas of employees is one of the causes of insufficient motivation to improve effectiveness, and thus the recognized need for improving efficiency. In the research they conducted, they cite insufficient involvement and insufficient motivation of employees as one of the obstacles to the implementation of the *lean* concept. In Bosnia and Herzegovina for healthcare institutions, a frequent obstacle to the implementation of modern models is the lack of motivation. In British and Dutch hospitals, recognized wastages are eliminated through modern improvement concepts, and in BH they are found without sufficient implementation, but the encouraging data is that in 43 cases interest in implementation is spreading. Adequate knowledge of business processes is necessary for the implementation of the lean concept in healthcare. In order to achieve an increase in the effectiveness and efficiency of business processes, it is necessary to find process indicators. In the Britain and Dutch hospitals, integral indicators are applied: process ef-

ficiency and workforce productivity. In BH health institutions, it is necessary to work more on determining indicators, above all the productivity of the workforce, which is aimed at reducing defects that are part of everyday business according to the results of the research.

According to [13,14]. characteristic of the situation and problems in health care systems, the solution lies in the implementation of modern business process improvement concepts. In addition to them, the following are specifically mentioned as *lean* indicators: cycle efficiency, cycle time, overall equipment effectiveness. The respondents in this research rated 80% of cases as significant and very significant (*table 3*), which confirms the possibility of applying the indicator as in Dutch and British hospitals. In support of this, the results on *graph 1* show how employees at the tertiary level of health care see the implementation of the *lean* concept. The effects that the respondents expect to achieve through the implementation of the *lean* concept to a significant extent coincide with the effects that are evident in hospitals that apply the *lean* concept. As many 76% of the respondents agree that the waiting time for documentation of patient placement in hospitals would be reduced, in 64% of cases, waiting lists of patients would be checked more quickly, in 58% of cases the medical staff would be more productive, in 52% of cases the flow of resources would be more efficient.

Also, the mentioned research results confirm that the implementation of the *lean* concept of improving business processes would solve medical wastages, which are listed as categories of transport, waiting and movement in (table 4). With the mentioned results of the research, the respondents confirmed their agreement that the mentioned defects would be eliminated by the implementation of the lean concept. Correcting errors would certainly result in an increase in: patient satisfaction, faster checking of patient waiting lists, reduction of waiting time for hospital admissions, reduction of administrative costs and losses. In order to analyze waste, it is necessary to define process indicators. In our research of the oncology department, to precisely define the indicators, this would determine the cause and eliminate waste more quickly. Although the implementation of the *lean* concept has proven to be successful in reducing waste in healthcare, surveys of hospital managers have shown that full implementation in healthcare in the Netherlands is still not high. Philips Healthcare Consulting divided the reasons into three main ones, based on the results of research conducted in 77 Dutch hospitals. It was determined that full implementation in healthcare is low due to: lack of resources (59% of respondents), insufficient information (41% of respondents), and insufficiently developed management models (30% of respondents).

Conclusion

This research was conducted to determine the level of understanding of the importance and possibility of applying the *lean* concept at the tertiary level of health care. Health workers in the highest percentage of agreement indicated that the implementation would achieve greater effectiveness and efficiency of business processes. This would mean: reducing the waiting time for documents for hospitalization of patients, increasing the productivity of employees, reducing the inefficient flow of employees and resources and easier checking of the waiting list. In research of potential benefits of the implementation of the *lean* concept, it was determined that healthcare workers recognize the importance of the *lean* concept, but in order to encourage them to implement it, education and seminars are needed. And on the other hand, healthcare management needs to prepare a *lean* concept implementation strategy**.**

In the healthcare system, the implementation of contemporary concepts is very important, from the aspect of timely execution of all the demands defined by the end user (patient). In this study, the initial premise was that, in order to improve the clinical process, it is necessary to minimize errors and improve service delivery through decreased waiting time. This confirms the basic premise of the method – the rationalization of the clinical process.

The success of healthcare organizations is in direct correlation with the quality of the resources used to provide services [15, 16]. To achieve that effect , it is necessary to use tools that enable the control of resource expenditure.

The contribution of this research is updating the topic of the necessity of implementing modern business process improvement concepts in order to improve health services for patients at the tertiary level of health care.

References

1. Mazur M, Momeni H. LEAN Production issues in the organization of the company - the first stage, Production engineering archives, 2018;21 (4):36-39.
2. Khamidullina M. A, Puryaev SA. Study of lean production technology application at domestic and foreign enterprises, Academy of Strategic Management Journal, 2017;15(1); 61-66.
3. Brown C. Why and how to employ the SIPOC model. J Bus Contin Emer Plan. 2019 Jan 1;12(3):198-210.
4. Sharma P, Gupta A, Malik SC, Jha PC. Quality Improvement In Manufacturing Process Through Six Sigma: A Case Study Of Indian MSME Firm. Yugoslav Journal of Operations Research 2019; 29(4):519–537.
5. Hadek A, Bakkali S, Ajana S. Sipoc Model In Moroccan Engineering Education Context: Lean Approach. International Journal of Education 2019;7(1):47–60.
6. Chyon BSc FA, Ahmmed BSc MS, Shuvo BSc MKA, Suman BSc MNH, Hossain PhD MM. Measuring Process Capability in a Hospital by Using Lean Six Sigma Tools-A Case Study in Bangladesh. Glob Adv Health Med. 2020 Oct 8;9:2164956120962441.
7. Reshad AI, Rahman MM, Chowdhury NM. Performance of Epidemic Healthcare Management during COVID-19 Outbreak using LSS DMAIC Approach: A Case Study for Bangladesh. Proceedings of the 5th NA International Conference on Industrial Engineering and Operations Management, Detroit, Michigan, USA, August 10 - 14, 2020.
8. Dickson EW, Anguelov Z, Vetterick D, Eller A, Singh S. Use of lean in the emergency department: a case series of 4 hospitals. Ann Emerg Med. 2009 Oct;54(4):504-1
9. Radnor ZJ, Holweg M, Waring J. Lean in healthcare: the unfilled promise? Soc Sci Med. 2012 Feb;74(3):364-371.
10. Stoiljković V. Lean u Zdravstvu Srbije. [Internet]. [Accessed: June 7, 2022]. Available from: http://www.cimlss.rs/wp-content/uploads/2014/08/Lean-u-Zdravstvu.pdf.
11. Ambler T. Marketing and the Bottom Line. 2nd ed. Harlow, UK: Financial Times Prentice Hall; 2003.
12. Piškor M, Kondić V. Lean production kao jedan od načina povećanja konkurentnosti hrvatskih poduzeća na globalnom tržištu. Tehnički glasnik. 2010;4(1-2):37-41. [Internet]. [pristupljeno 07.07.2022.]. Available from: https://hrcak.srce.hr/85887.
13. Mićović, P. Mneadžment zdravstvenog sistema. Evropski centar za mir i razvoj ECPD Univerziteta za mir Ujedinjenih nacija, 2000.
14. Radnor, Z. J., Holweg, M., Waring, J. Lean in healthcare: The unfilled promise? Social Science & Medicine, 2012 (LXXIV);364-371.
15. Narkhede B. E, Raut R. D, Roy M, Yadav V. S, Gardas B. Implementation barriers to lean-agile manufacturing systems for original equipment manufacturers: an integrated decision-making approach, The International Journal of Advanced Manufacturing Technology, 2020; 108 (9); 3193-3206.
16. Jin, R., Hancock, C., Tang, L., Chen, C., Wanatowski, D., Asce, M. and Yang, L. Empirical study of BIM implementation – based perceptions among Chinese practitioners", Journal of Management in Engineering, 2017; 33(5); 1-11.
17. Zhang, L., Chen, X. and Suo, Y. Interrelationships among critical factors of work flow reliability in lean construction", Journal of Civil Engineering and Management, 2017;23(5);621-632.
18. Bonavía T, Marín JA. An empirical study of lean production in the ceramic tile industry in Spain. Int J Oper Prod Manag. 2006 May 1;26(5):505-31.
19. Holden RJ. Lean Thinking in emergency departments: a critical review. Ann Emerg Med. 2011 Mar;57(3):265-78.
20. Successfully deploying Lean in healthcare. Philips Healthcare. [Internet]. [Accessed: 18.5.2022.]. Available from: https://www.philips.be.
21. Mićović PM, Jakovljević Đ, Dovijanić P. Zdravstveni menadžment: menadžment zdravstvenog sistema i zdravstvenih ustanova. Beograd: Komora zdravstvenih ustanova Srbije; 2008.
22. Jae YM, Byeong WK, Young HS, Choon SL, Hyungjoon M. An integrated Method for Business Process Improvement. Int J Innov Comput Inf Control. 2012 July 8(7(B)):5237-50.
23. Jin, R., Hancock, C., Tang, L., Chen, C., Wanatowski, D., Asce, M. and Yang, L. Empirical study of BIM implementation – based perceptions among Chinese practitioners", Journal of Management in Engineering, 2017; 33(5); 1-11.
24. Zhang, L., Chen, X. and Suo, Y. Interrelationships among critical factors of work flow reliability in lean construction", Journal of Civil Engineering and Management, 2017;23(5);621-632.
25. Senouci, A., Ismail, A. and Eldin, N. Time delay and cost overrun in qatari public construction projects", Procedia Engineering, (June), 2016;164; 368-375.
26. Sarhan, J.G., Xia, B., Fawzia, S., Karim, A. and Olanipekun, A. Barriers to implementing lean construction practices in the Kingdom of Saudi Arabia (KSA) construction industry", Construction Innovation, 2018; 18(2) 246-272.
27. Sharma P, Gupta A, Malik SC, Jha PC. Quality Improvement In Manufacturing Process Through Six Sigma: A Case Study Of Indian MSME Firm. Yugoslav Journal of Operations Research 2019; 29(4):519–537.

Posterior circulation ischaemic stroke - A retrospective analysis from a General Hospital

Frederic-Ivan Silconi[*1], Marijana Radić[1], Ivan Jovanović[2], Dolores Janko-Labinac[1], Nevia Novak[1], Petra Cukon[1]

[1] Department of Neurology, General Hospital Pula, Croatia.
[2] Department of Radiology, University Hospital Centre Zagreb, Croatia.

Abstract:

Even though ischemic stroke represents a majority of strokes in general, only a smaller portion originate from posterior circulation. Because of different origin and particular territory involvement, this represents a difficult clinical task. We compared relevant clinical data from literature with results of our patients affected by the posterior circulation stroke (PCS). We analyzed stroke patients admitted from 2018. to 2022. in General Hospital Pula, a touristic oriented county hospital in Croatia on the Adriatic Coast. In that five-year period we admitted 1795 patients with ischemic stroke. 246 or 13,6% of those originated from the posterior circulation, which is significantly less than data from similar reports. Majority of those patients were male, 64%. Comparing the outcome, we found that the PCS had significantly better outcome. Mortality rate was similar in both,14% for PCS versus 16% in the anterior circulation strokes (ACS). We analyzed the outcome by infarct region or etiology, as well as clinical particularities related to the territory of PCS involvement. We also selected patients having PCS as a result of dissection. According to our results the patients with PCS had better outcome in comparison to ACS. The most frequent site of stroke was cerebellar, followed by pontine stroke. The highest mortality was observed in patients with multiple posterior circulation strokes. Initial NIHSS score was lower in posterior circulation strokes then in anterior circulation strokes, with an important impact on reperfusion therapy rates. Therefore, it is crucial to perform comprehensive clinical evaluation of patients with posterior circulation ischemic strokes.

Key words: Posterior circulation stroke, Anterior circulation stroke, National Institutes of Health Stroke Scale (NIHSS), Risk factors, Modified Rankin Score (mRS)

Keywords: Posterior circulation stroke, Anterior circulation stroke, National Institutes of Health Stroke Scale (NIHSS), Risk factors, Modified Rankin Score (mRS)

Sažetak:

Ishemijski moždani udar stražnje cirkulacije - retrospektivna analiza iz opće bolnice

Iako ishemijski moždani udar predstavlja većinu moždanih udara općenito, samo manji dio potječe iz stražnje cirkulacije. Zbog različitog podrijetla i zahvaćenosti određenog teritorija, ovo predstavlja težak klinički zadatak. Usporedili smo relevantne kliničke podatke iz literature s rezultatima naših pacijenata pogođenih moždanim udarom stražnje cirkulacije (PCS). Analizirali smo pacijente s moždanim udarom primljene od 2018. do 2022. godine u Općoj bolnici Pula, turističko orijentiranoj županijskoj bolnici u Hrvatskoj na jadranskoj obali. U tom petogodišnjem razdoblju primljeno je 1795 bolesnika

OPEN ACCESS

Correspondence:
Frederic-Ivan Silconi
fsilconi@hotmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 15 May 2023
Accepted: 01 June 2023
Published: 26 June 2023

Citation:
Silconi F-I, Radić M, Jovanović I, Janko-Labinac D, Novak N, Cukon P. Posterior circulation ischaemic stroke - A retrospective analysis from a General Hospital RAD CASA - Medical Sciences. 556=62-63 (2023): 44-53
DOI: 10.21857/90836cz5wy

s ishemijskim moždanim udarom. 246 ili 13,6% potječe iz stražnje cirkulacije, što je znatno manje od podataka iz sličnih izvješća. Većina tih pacijenata bili su muškarci, 64%. Uspoređujući ishod, otkrili smo da je PCS imao značajno bolji ishod. Stopa smrtnosti bila je slična u oba, 14% za PCS naspram 16% za udare prednje cirkulacije (ACS). Analizirali smo ishod prema regiji infarkta ili etiologiji, kao i kliničkim posebnostima vezanima uz područje zahvaćenosti PCS-a. Također smo odabrali pacijente koji imaju PCS kao posljedicu disekcije. Prema našim rezultatima bolesnici s PCS-om imali su bolji ishod u usporedbi s ACS-om. Najčešće mjesto moždanog udara bio je cerebelarni, a zatim moždani udar mosta. Najveća smrtnost zabilježena je u bolesnika s višestrukim moždanim udarima stražnje cirkulacije. Početni NIHSS rezultat bio je niži u udarima stražnje cirkulacije nego u udarima prednje cirkulacije, s važnim utjecajem na stope reperfuzijske terapije. Stoga je ključno provesti sveobuhvatnu kliničku procjenu bolesnika s ishemijskim moždanim udarom stražnje cirkulacije.

Ključne riječi: moždani udar stražnje cirkulacije, moždani udar prednje cirkulacije, ocjenska ljestvica moždanog udara Nacionalnog instituta za zdravlje (NIHSS), faktori rizika, modificirani Rankinov score (mRS)

Introduction

The majority of ischemic strokes occurs in the territory of the anterior circulation. 20% to 25% of ischemic strokes are from the posterior circulation (1). Mortality rates of those strokes vary from 3,6% to 18,6% (2).

Posterior circulation ischemia (PCI) involves respectively the proximal division, irrigated by the vertebral artery (VA) and the posterior inferior cerebellar artery (PICA), the middle division with the basilar artery (BA) and the anterior inferior cerebellar artery (AICA) and finally the most frequent, the distal division, irrigated by the posterior cerebellar artery (PCA) and the superior cerebellar artery (SCA) with the penetrating branches of BA and PCA (2,3,4). (Figure 1.)

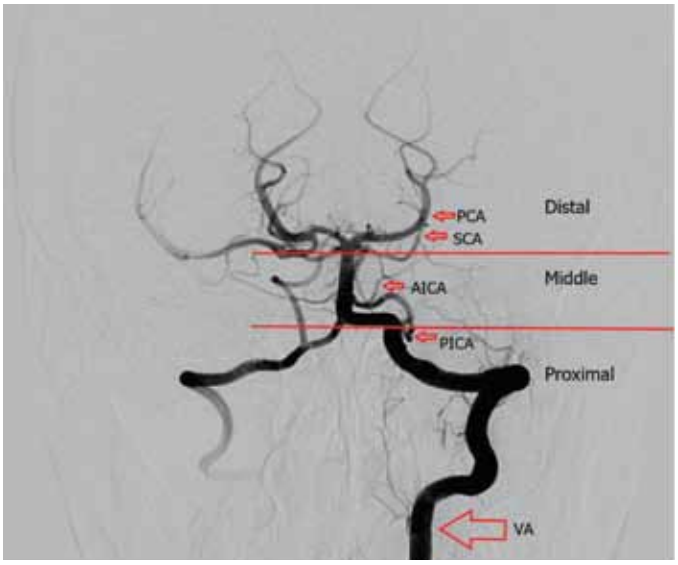


Figure 1. Anteroposterior projection DSA image of the left vertebral artery. Courtesy of I. Jovanović MD PhD, Department of Radiology, University Hospital Centre Zagreb

According to the study by Searls et al. the most common areas of PCS by proportion are distal (41%), multiple territories (25%), proximal (18%) and middle (16%) (3). Posterior circulation irrigation involves the brainstem, including the medulla oblongata, pons and midbrain, the cerebellum, thalamus, the occipital cortex, the medial temporal cortex, and part of the parietal lobe. According to the previously mentioned study, analyzing symptoms and signs of PCI of 407 patients recruited in the New England Medical Center Posterior Circulation Registry, the most frequent symptoms were dizziness (41%), unilateral limb weakness (41%), dysarthria (31%), headache (28%), nausea and vomiting (27%) (3). The most frequent sign was unilateral limb weakness (38%), followed by gait ataxia (31%), unilateral limb ataxia (30%) dysarthria (28%) and nystagmus (24%). The same study found a positive correlation of dysphagia, nausea, vomiting, dizziness and Horner syndrome with the proximal posterior vascular territory, unilateral limb weakness and cranial nerve VII deficit with the middle territory and finally limb sensory deficit lethargy and visual loss positively correlate with the distal territory (3). You may notice that those frequent signs from a proximal territory belong to the lateral medullary syndrome or Wallenberg syndrome.

Generally, posterior circulation stroke events result in a better outcome than anterior circulation stroke. According to the New England Medical Center Posterior Circulation Registry, poor outcome was observed in 3,6% of patients, comparable to study by Bogousslavsky et al., showing 30-day mortality rate of

5,9% in a population of 1000 patients from the Lausanne Stroke Registry (5,6). A similar low mortality rate of 3% was reported recently by Han Y. et al. after a one-year follow up. The same study has established poor outcome (mRs 3 or larger) in 15.2% of 165 patients (7). Poor outcome in studies by Caplan et al. and Glass was more frequently related to distal territory lesions, up to 77% (2,4). The relative risk (RR) of poor outcome was higher in distal territory ischemia (3,12), compared to 1,88 for middle territory and 0,81 for proximal territory (4).

These results are in coherence with study by Hacke et al. showing a 70% mortality rate in comatose or tetraplegic patients with proven intracranial vertebral artery (ICVA) or basilar artery (BA) occlusion (8). Age, alcohol abuse and previous stroke were associated with a worse outcome. The RR of worse outcome was significantly lower for large artery disease (0,59), compared to cardioembolic stroke (1,89). Finally, multiple infarcts were also more frequently associated with a worse outcome, with reports of 60,5% patients with poor outcome having three brain lesions (4).

Stroke etiology study performed on 407 patients from the New England Medical Center Posterior Circulation Registry (NEMC-PCR) by Caplan et al. showed that the most common posterior circulation stroke mechanism was embolic in 40% of cases, of which 24% were of cardiac source and 14% of arterial. Large artery occlusive disease accounted for 32%, perforating and circumferential branch occlusion was the reason for 14% of PCS, migraine 3% and 10% by other reason (2).

Besides the previously mentioned classification in three divisions, posterior circulation was further divided into six groups by Bogousslavsky et al. in 1988: brainstem, cerebellum, superficial, deep (thalamus), PCA territory and multiple location. Forty-eight percent of the vertebrobasilar infarcts were in the brainstem (mainly pons in 27%, mainly medulla in 14%, mainly midbrain in 7%), 7% in the cerebellum, 36% in the PCA territory (entire territory in 7%, deep in 11%, superficial in 18%), and 9% in multiple locations (5). The presumed causes of infarction in this study were defined as atherosclerosis with or without stenosis, embolic heart disease, hypertensive arteriopathy, mixed etiologies, other etiologies like dissections and finally undetermined etiology. Embolic lesions were most frequently present in the cerebellum and in infarcts of multiple locations. Dissections most frequently resulted in brainstem ischemia, they were more prevalent in younger patients and usually posttraumatic by origin (5).

Probably 20% of blood flow belongs to the vertebrobasilar vascular territory (9). That would mean that one in five embolic strokes originate from the posterior circulation. However it has to be considered the geometry of vertebral arteries, their origin and the diameter as opposed to the carotid arteries which may increase the risk of focal atherosclerosis (10). There is a higher frequency of anatomical variants in the vertebrobasilar circulation- mostly fetal variant of artery communication in the PCA and VA hypoplasia. (11 12). For example the VA hypoplasia was observed more frequently in strokes affecting the PICA. There were not an increased risc of strokes in the fetal PCA. (12.)

The National Institutes of Health Stroke Scale (NIHSS) is the most commonly used scale to validate stroke severity, intended mostly for rt-PA and endovascular intervention, but also indispensable in stroke research. NIHSS correlates with infarct size, clinical severity, and long-term outcome (13). NIHSS scale cut-off for favorable outcome is lower in posterior circulation strokes. An analysis showed important differences between median NIHSS values, median value for AC stroke was seven, compared to two in PC strokes. This study also showed that the majority of PC strokes had a NIHSS score of 4 or less and 15% of those strokes had a poor outcome (14). This suggests that NIHSS underestimates clinical severity in posterior circulation stroke and patients presenting with low NIHSS may wrongly be considered ineligible for reperfusion therapy.

It is known that the questionnaire is more oriented toward the anterior circulation lesions, examines mostly motor and cortical functions, especially language, and contains fewer questions about dysphagia, nystagmus, truncal ataxia or cranial nerve lesions with exemption of facial nerve. Even though a modified version of NIHSS scale showed higher prognostic accuracy and usefulness to identify posterior circulation stroke patients with low NIHSS score and higher risk of poor outcome, it hasn't been widely accepted in any form (15).

Subjects and Methods

In this retrospective study we analyzed all ischemic stroke patients admitted to General Hospital Pula in the period between 2018 and 2022. Patients were divided into two main groups, anterior circulation and posterior circulation strokes. In both groups we recorded the following epidemiological data for each patient: sex, age, initial NIHSS at admission, presence or history of atrial fibrillation (AF), administered revascularization therapy and the modified Rankin scale (mRs) after discharge. Poor outcome was defined as mRS 3 to 6 at 3 months from discharge. We particularly studied our posterior circulation stroke patients, examining data about symptoms and signs, defined risk factors such as hypertension, diabetes, hyperlipidemia, AF; and presumed etiology. We identified the involved artery and territory in the posterior circulation stroke. The territories involved were the occipital lobe and other less common cortical lobes, the thalamus, midbrain, pons, medulla oblongata and the cerebellum. The territory of the cerebellum as the widest and in our study the most frequent stroke location was further stratified in subgroups such as VA territory stroke, PICA stroke, AICA or SCA stroke. In addition to these single territories, we also recorded cases with multiple territory involvement.

Quantitative data are expressed as mean ± standard deviation (SD). Qualitative data are expressed as frequency and percentage. Statistical analysis was performed by univariate regression analysis, followed by multivariate logistic regression analysis. A value of $P < 0.05$ was considered statistically significant.

Results

During the five-year period we treated 1549 anterior circulation stroke patients and 246 posterior circulation patients. Over that period we noticed a kind of convergence: the numbers of ACS through those years slowly dropped but PCS seemed to rise in number of cases, though it was not statistically significant (Figure 2.).

Among 1549 ACS patients 818 or 52,81% were women, difference is significant (chi-square test x^2 4,89; p 0,027). Among 246 PCS patients there were significantly less women than men – we observed 88 or 35,77% of women, according to chi-quadrat test x^2 value was 19,9; p less than 0,001 (Table 1.).

Figure 2. Ischemic strokes in general Hospital Pula between 2018 and 2022.

Table 1. Differences of age onset between female and male.

	ACS			PCS			
N.1549	mean	Range	SD	N.246	mean	Range	SD
All	78	22-100	11,79		69	46-89	11,5
Female	82	22-100	11,52		75	46-89	9,45
Male	73	30-98	11		67,5	30-97	12

In both ACS and PCS groups male patients were younger, p<0,001. The percentage of PCS in the pool of ischemic stroke patients was lower than usual: 13.6%.

Age stratification showed differences between the two types of stroke: PCS patients were younger, with largest proportion in the middle aged group. Greater number of ACS cases occurred in the elderly age (Figure 3.).

In ACS and PCS groups of patients atrial fibrillation was more often present in the female patients (Table 2.).

As shown in (Table 3.), at admission PCS patients had, according to NIHSS value, a less pronounced deficit and also a better outcome later. Results showed lower death rate in the PCS group.

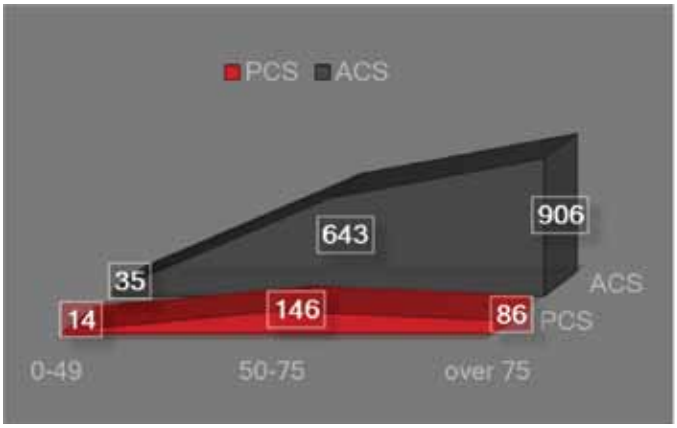


Figure 3. Age stratification for PCS and ACS.

Table 2. Incidence of atrial fibrillation between sexes.

	Sex		Chi-quadrat	p		Sex		Chi-quadrat	p
A C S	Male	197 (27%)	22,38	p<0,001	P C S	Male	33 (20,89%)	11,23	0,0008
	Female	313 (38,3%)				Female	36 (40,91%)		

Table 3. Epidemiology of posterior circulation stroke, PCS and anterior circulation stroke, ACS.

	PCS n. 246	ACS n. 1549	Ischemic stroke
Mean age (range)	70 (38-97)	76 (22-100)	73
Gender F/M n. (%)	88/158 36/64%	818/1549 53/47%	906/1794 51 (49%)
Mortality n. (%)	34/ (14%)	248 (16%)	282 (16%)
mRS 0-2 n. (%)	117 (48%)	499 (32%)	616 (32%)
AFib n. (%)	69 (28%)	510 (33%)	577 (32%)
NIHSS n. (%)	Mean: 7	Mean: 10	312 (17%)
NIHSS > 15	29 (12%)	283 (25%)	

We performed a multivariate regression analysis, more precisely logistic regression. In this model, we obtained a good predictive power of 83.41% for ACS group, when comparing the outcome with NIHSS, sex, age and AF. We found that Odds ratio for a bad outcome was 20,45. In the PCS patient group there was also a good predictive power of 76,02% but with a lower odds ratio for a bad outcome, 10,45. There was a twice bigger odd for a bad outcome in the group of ACS patients then in PCS patients. Logistic regression showed that NIHSS (p<<0.001, r=0.36) and age (p=0.003, r=0.04) significantly affect the outcome, while gender and FA are not significant predictors in case of PCS patients. (Table 4.).

Table 4. Comparison of predictors for outcome in ACS and PCS patients.

ACS	Logistic regression Predictive variables	Regressional coefficient	c^2=787 p<0,001
1	NIHSS	0,42	p<<0,001
2	Sex	0,33	P 0,03
3	Age	0,04	P <<0,001
4	Atrial fibrillation	0,01	0,928

PCS	Logistic regression Predictive variables	Regressional coefficient	c^2=100,65 p<0,001
1	NIHSS	0,36	<<0,001
2	Sex	0,11	0,74
3	Age	0,04	0,003
4	Atrial fibrillation	0,21	0,569

The most frequent symptom in PCS patients were dizziness (68%) and dysarthria in 59% of patients. The most frequent sign was dysarthria followed by limb ataxia. Cranial nerve involvement was also frequent, in 46% of patients (Table 5.).
It's notable that there were no statistically significant differences in occurrence of dysarthria depending on the location of affected vascular territory. According to the territory involved and corresponding leading sign we may say that the cerebellum where more related with ataxia, medulla with nystagmus, dysarthria and cranial nerve involvement meanwhile distal territories where more related with limb paresis. (Table 6.)

Table 5. symptoms and signs in PCS

Symptoms	n. (%)	Signs	n. (%)
Dizziness	169 (68%)	Unilateral limb weakness	108 (44%)
Unilateral limb weakness	132 (48%)	Gait ataxia	98 (40%)
Dysarthria	144 (59%)	Unilateral limb ataxia	132 (54%)
Headache	79 (32%)	Dysarthria	150 (61%)
Nausea and vomiting	117 (48%)	Nystagmus	61 (25%)
		Skin sensation impairment	57 (23%)
		Cranial nerve involvement	114 (46%)

Table 6. Most frequent signs in PCS.

Vascular territory	Most prominent sign	%
1. Midbrain	Cranial nerve palsy	63,6 %
2. Pons	Dysarthria	74 %
3. Medulla	Nystagmus, Cranial nerve palsy and dysarthria	63 %
4. Occipital lobe	Limb paresis	54 %
5. Thalamus	Limb paresis	69,6 %
6. Cerebellum	Limb and gait ataxia	68,9 %
7. Multiple territories	Limb paresis and dysarthria	62,5 %

Table 7. Territories involved as division involved in PCI.

Cerebellum	medulla	pons	midbrain	thalamus	Occipital lobe	Multiple location
74 (30%)	27 (11%)	50 (20%)	11 (4,5%)	23 (9,5%)	37 (15%)	24 (10%)

Proximal division	Middle division	Distal division	Multiple division
81 (33%)	70 (28%)	71 (29%)	24 (10%)

Most frequently affected territory was the cerebellum in 30% of PCS cases, followed by the pons in 20% of cases. Therefore, PCS was more frequent in the proximal territory. Distal territories were proportionally less involved in PCS (Table 7.).
When observing cerebellar infarcts particullarly, the most frequent was the PICA irrigated territory followed by the massive hemispheric infarction. Distal arteries were less frequently affected. Ischemic lesions in the territory of VA or PICA were more often related to atrial fibrillation. PICA territory infarct had the greatest incidence of AF, 41%. A good outcome for the cerebellar infarcts was present in 39% of patients, less than the average for PCS reported in literature (Fig 4).

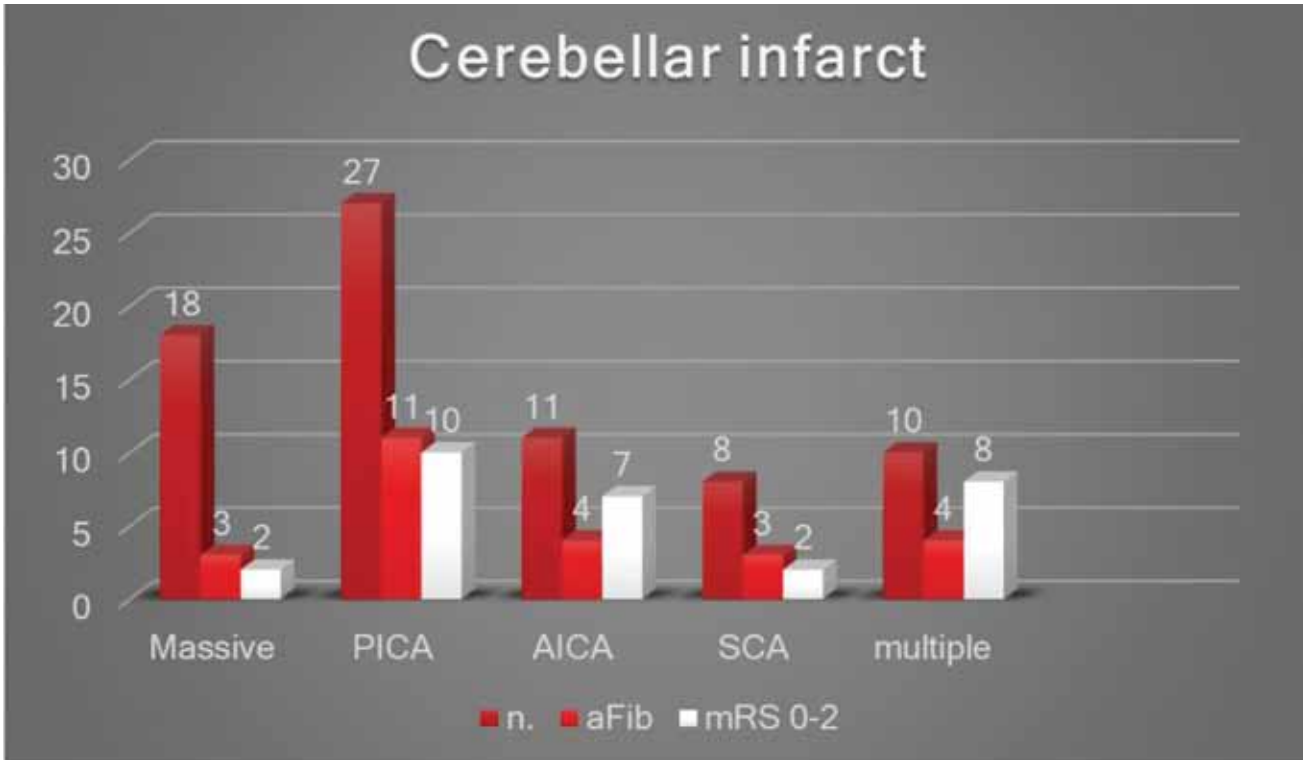


Figure 4. Distribution of patients with different cerebellar territory infarct, presence of aFib as a risc factor and good outcome in our PCS group (absolute numbers).

The most frequent risk factor was hypertension. There were fewer PCS patients with atrial fibrillation then ACS patients - 28% versus 32% of patients (Table 8).
Distribution of PCS by etiology in our cohort was respectively: embolic stroke, large artery disease, penetrating artery disease and dissections. Most frequently stroke was caused by emboli, 32%, 28% from a cardiac origin. Large artery disease was similarly frequent, in 28% of cases, followed by penetrating artery disease in 23% of cases. We had 10 patients with different dissections (4,2%), obviously involving proximal arteries like VA and PICA (Table 9).
In this analysis we didn't find a statistically positive relation between small vessel disease or perforator artery occlusion with common risk factors like hypertension, diabetes and hyperlipidemia (Table 10.).

Table 8. Risk factors in PCS.

Risk factor	n.	%
Hypertension	221	90
Diabetes mellitus	88	36
Hyperlipidemia	161	65
Atrial fibrillation	69	28

Table 9. Presumed etiology of PCS.

Etiology	GH Pula n. (%)
Large artery disease	68 (28%)
Embolism	78 (32%)
Cardiac source	69 (28%)
Penetrating artery disease	56 (23%)
Dissection	10 (4,2%) 7 VA, 2 PICA and 1 SCA

Table 10. Relation between common risc factors and small vessel disease.

	Risc HA	Risc DM	Risc HLP		P
Small vessel disease	78	33	62	0,39	0,822
No small vessel disese	142	55	99		

	Risc HA	Risc DM	Risc HLP		P
Perforator	46	25	34	2,30	0,316
No perforator	175	63	127		

Table 11. Differences between initial NIHSS of PCS and ACS patients.

N=246 PCS	median	Mode	First quartiles	Third quartiles	Standard deviation
NIHSS	4,5	3	3	8	6,24
N=1549 ACS					
NIHSS	8	6	5	14	5,95

If we look back to NIHSS values in our cohort there was a substantial difference between the two stroke groups.(Table 11.) Following median and mean NIHSS values for PCS, most of those patients wouldn't be eligible for revascularization treatment. Our experience is quite disappointing, while our rt-PA rates are up to 9,7% of ischemic stroke, only 3,7% (n. 9) of PCS patients were treated with rt-PA, none with MT. According to a larger collaborative study, minor PCS are significantly more often associated with disability at 3 months compared to minor ACS (16). We also had similar conclusions: out of 121 patients with NIHSS ≤4, 33 or 28% had a poor outcome, meanwhile 65 of 339 or only 19% from the ACS group also had a poor outcome.

Discussion

We wanted to compare our results with previously published studies regarding this still challenging part of cerebral ischemia research, the posterior circulation stroke. During these five years, we have seen a small but increasing number of strokes in the posterior circulation. These epidemiological data, although in many aspects not statistically significant, can definitely predict a new trend and show that it is necessary to pay more attention to the differentiation of this type of stroke. We demonstrated that the posterior circulation stroke is more likely to affect younger patients, another reason to put more effort into not underestimating the clinical presentation. As we know from other studies, this clinical presentation can vary and usually leads to the misinterpretation of a mild stroke. The NIHSS values in PCS patients are shown to be lower than in ACS. According to our finding more PCS patients with low initial NIHSS scoring (≤4) had a worst outcome (mRS ≥3) compared to ACS patients. Although, in general, we had better outcomes and lower mortality rates in PCS group. Atrial fibrillation as a major cause of embolic stroke was not as prominent in our study as expected or observed in other studies. This may be because our posterior circulation strokes occurred in the proximal territory rather than in the distal territory, where they have been mostly shown to originate from embolic propagation. In our study, the cerebellum was the most common site, especially the PICA, although with a particularly high rate of atrial fibrillation, leading to the conclusion that etiologically these strokes also had a cardioembolic etiology, after all. This statement differs from data from other studies, and the reason could perhaps be a combined lesion in the proximal part of the vertebrobasilar territory. Reviewing our medical records, we weren't able to capture all planned data, therefore there is a possibility of bias in data collection. According to our data 76% of our patients had angiography performed (MRIA or MSCTA) and only 45% had an MRI performed during the inpatient stay. We should have performed more neuroradiological and vascular examinations to clearly define any large vessel disease, especially in the ICVA and PICA, to determine the exact extent of LVD. Given the emerging therapeutic options, these patients should receive a detailed clinical evaluation and complete imaging of the brain and vessels, regardless of severity. Neurosonologic evaluation should be performed as soon as possible but not delaying therapy. In our study 75% of our PCS patients had a neurosonologic workup done. In view of the more frequent cardioembolic strokes in the posterior circulation, a complete cardiac evaluation is essential. Medical care should be particularly careful to assess dysphagia in order to prevent aspiration (17).
Finally, it should be said at the outset that it is critical to change the way we perform initial scoring to assess the severity of posterior circulation stroke. So far, there have been attempts to assign some value to certain signs such as dysphagia, abnormal coughing and gait ataxia but so far such ideas have not been broadly accepted. Perhaps with further adaptation of the NIHSS, we might reach a generally accepted consensus.

Acknowledgements

none

Conflict of interest

None to declare.

Funding sources

None.

References

1. Merwick A, Werring D. Posterior circulation ischaemic stroke. Bmj. 2014; 348:g 3175
2. Caplan L, Chung CS, Wityk R, et al. New England medical center posterior circulation stroke registry: I. Methods, data base, distribution of brain lesions, stroke mechanisms, and outcomes. J Clin Neurol. Apr 2005;1(1):14-30.
3. Searls DE, Pazdera L, Korbel E, Vysata O, Caplan LR. Symptoms and signs of posterior circulation ischemia in the new England medical center posterior circulation registry. Arch Neurol. 2012 Mar;69(3):346-51. doi: 10.1001/archneurol.2011.2083. Epub 2011 Nov 14. PMID: 22083796.
4. Glass TA, Hennessey PM, Pazdera L, et al. Outcome at 30 Days in the New England Medical Center Posterior Circulation Registry. *Arch Neurol.* 2002;59(3):369–376. doi:10.1001/archneur.59.3.369
5. Bogousslavsky J, Van Melle G, Regli F. The Lausanne Stroke Registry: analysis of 1,000 consecutive patients with first stroke. Stroke. 1988;19:1083-109
6. Bogousslavsky J, Regli F, Maeder P, Meuli R, Nader J. The etiology of posterior circulation infarcts: a prospective study using magnetic resonance imaging and magnetic resonance angiography. *Neurology*. 1993;43(8):1528-1533. doi:10.1212/wnl.43.8.1528
7. Han Y, Xu M, Zhao Y, Zhang Y. Long-term outcome and prognostic factors of posterior circulation ischemia patients: Results from a single center retrospective study. *Vascular*. 2020;28(1):25-30. doi:10.1177/1708538119866604
8. Hacke W, Zeumer H, Ferbert A, Bruckmann H, del Zoppo GJ. Intra-arterial thrombolytic therapy improves outcome in patients with acute vertebrobasilar occlusive disease. Stroke. 1988;19:1216-122 Posterior Circulation Ischemia:
9. Boyajian RA, Schwend RB, Wolfe MM, Bickerton RE, Otis SM. Measurement of anterior and posterior circulation flow contributions to cerebral blood flow. an ultrasound-derived volumetric flow analysis. *J Neuroimaging.* (1995) 5:1–3. doi: 10.1111/jon1995511
10. Ravensbergen J, Krijger JKB, Hillen B. The influence of the angle of confluence on the flow in a vertebrobasilar junction model. J Biomec. (1996) 29:281–99. doi: 10.1016/0021-9290(95)00064-X
11. van Raamt AF, Mali WP, van Laar PJ, van der Graaf Y. The fetal variant of the circle of Willis and its influence on the cerebral collateral circulation. Cerebrovasc Dis. (2006) 22:217–24. doi: 10.1159/000094007
12. Thierfelder KM, Baumann AB, Sommer WH, Armbruster M, Opherk C, Janssen H, et al. Vertebral artery hypoplasia: frequency and effect on cerebellar blood flow characteristics. Stroke. (2014) 45:1363–8. doi: 10.1161/STROKEAHA.113.004188
13. Brott T, Adams HP Jr, Olinger CP, et al. Measurements of acute cerebral infarction: A clinical examination scale. Stroke. 1989; 20:864–870. [PubMed: 2749846]
14. Inoa V, Aron AW, Staff I, Fortunato G, Sansing LH. Lower NIH stroke scale scores are required to accurately predict a good prognosis in posterior circulation stroke. Cerebrovasc Dis. 2014;37(4):251-5. doi: 10.1159/000358869. Epub 2014 Mar 25. PMID: 24686370; PMCID: PMC4956480.
15. Alemseged F, Rocco A, Arba F, Schwabova JP, Wu T, Cavicchia L, Ng F, Ng JL, Zhao H, Williams C, Sallustio F, Balabanski AH, Tomek A, Parson MW, Mitchell PJ, Diomedi M, Yassi N, Churilov L, Davis SM, Campbell BCV; Basilar Artery Treatment and Management (BATMAN) Collaboration Investigators. Posterior National Institutes of Health Stroke Scale Improves Prognostic Accuracy in Posterior Circulation Stroke. Stroke. 2022 Apr;53(4):1247-1255. doi: 10.1161/STROKEAHA.120.034019. Epub 2021 Dec 15. PMID: 34905944.
16. Kim JT, Park MS, Choi KH, Kim BJ, Han MK, Park TH, Park SS, Lee KB, Lee BC, Yu KH, Oh MS, Cha JK, Kim DH, Nah HW, Lee J, Lee SJ, Ko Y, Kim JG, Park JM, Kang K, Cho YJ, Hong KS, Choi JC, Kim DE, Ryu WS, Shin DI, Yeo MJ, Kim WJ, Lee J, Lee JS, Bae HJ, Saver JL, Cho KH. Clinical Outcomes of Posterior Versus Anterior Circulation Infarction With Low National Institutes of Health Stroke Scale Scores. Stroke. 2017 Jan;48(1):55-62. doi: 10.1161/STROKEAHA.116.013432. Epub 2016 Nov 17. PMID: 27856952.
17. Caplan L. Posterior circulation ischemia: then, now, and tomorrow. The Thomas Willis Lecture-2000. *Stroke*. 2000;31(8):2011-2023. doi:10.1161/01.str.31.8.2011

Effect of intrathecal morphine on pain score in total hip arthroplasty

Anja Mandarić*[1], Zrinka Orešković[1], Ivan Marić[2], Marijana Žura[1], Sandra Morović[3]

[1] University Hospital Centre Zagreb, Department of Anaesthesiology, ICU and Pain Therapy
[2] Clinical Hospital Dubrava, Department for Orthopaedics and Traumatology, Clinic for surgery
[3] Aviva Medical Centre

Abstract:

Introduction: The advantage of intrathecal morphine is due to its delivery into the subarachnoid space with direct access to opiate receptors and ion channels, while clinical duration of action can be as long as 20 hours. Joint replacement surgery is reported to be one of the most painful surgical procedures. The key factor for short postoperative length of stay and rapid functional recovery is pre-operative, intraoperative and postoperative analgesia. Spinal anaesthesia incorporating intrathecal morphine has been used as a systemic opioid-sparing technique. The most frequently investigated dose of intrathecal morphine was 100 µg.

Materials and Methods: In this study, spinal anaesthesia with the addition of morphine for intrathecal administration at a dose of 200 µg and 250 µg was administered to patients who underwent surgery for total hip arthroplasty and VAS pain scale was monitored postoperatively in the next 24 hours. The study group was compared to a group of patients who received standard intravenous analgesia postoperatively.

Results: Intrathecal application of morphine improves pain management in the first 24 postoperative hours in comparison to a control group who has received a systemic combination of opioid and non-opioid analgesics as part of postoperative analgesia.

Conclusions: The use of intrathecal morphine at a dose of 200 µg or 250 µg is an extremely good analgesic method in the postoperative period after surgery for total hip arthroplasty.

Keywords: Intrathecal, Hip arthroplasty, Morphine, Pain management, Regional anaesthesia

Sažetak:

Učinak intratekalnog morfija na skalu boli kod operativnog zahvata ugradnje totalne endoproteze kuka

Uvod: Prednost primjene intratekalnog morfija je njegova isporuka u subarahnoidalni prostor s izravnim pristupom opioidnim receptorima i ionskim kanalima a kliničko djelovanje može biti i do 20 sati. Operativni zahvat ugradnje totalne endoproteze kuka smatra se jednim od najbolnijih kirurških zahvata u medicini. Ključni čimbenik kratkog postoperativnog boravka i brzog funkcionalnog oporavka je preoperativna, intraoperativna i postoperativna analgezija. Spinalna anestezija koja uključuje intratekalni morfij korištena je kao sustavna tehnika koja smanjuje upotrebu opioida intravenski. Najčešće ispitivana doza intratekalnog morfija je 100 µg.

Materijali i metode: Kod bolesnika koji su podvrgnuti operativnom zahvatu ugradnje totalne endopro-

OPEN ACCESS

Correspondence:
Anja Mandarić
anja.mandaric2@gmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 15 January 2023
Accepted: 15 April 2023
Published: 26 June 2023

Citation:
Mandarić A, Orešković Z, Marić I, Žura M, Morović S. Effect of intrathecal morphine on pain score in total hip arthroplasty 556=62-63 (2023): 54-58
DOI: 10.21857/m8vqrtgl09

teze kuka primijenjena je spinalna anestezija s dodatkom morfija za intratekalnu primjenu u dozi od 200 µg i 250 µg te je praćena VAS skala boli 24 sata postoperativno. Ispitivana skupina uspoređena je sa skupinom bolesnika koji su postoperativno primali standardnu intravensku analgeziju.
Rezultati: Intratekalna primjena morfija efikasnije smanjuje subjektivni osjećaj boli u prva 24 postoperativna sata u usporedbi s kontrolnom skupinom koja je primala sistemsku kombinaciju opioidnih i neopioidnih analgetika kao dio postoperativne analgezije.
Zaključak: Primjena intratekalnog morfija u dozi od 200 µg i 250 µg izuzetno je dobra analgetska metoda u postoperativnom razdoblju nakon operacije ugradnje totalne endoproteze kuka.

Ključne riječi: endoproteza kuka, intratekalni morfij, liječenje boli, regionalna anestezija

Introduction

The advantage of intrathecal morphine is due to its delivery into the subarachnoid space with direct access to opiate receptors and ion channels. Clinical duration of action can be as long as 20 hours given the biphasic pattern.
Joint replacement surgery is reported to be one of the most painful surgical procedures. The key factor for short postoperative length of stay and rapid functional recovery is pre-operative, intraoperative and postoperative analgesia (1). Spinal anaesthesia incorporating intrathecal morphine has been used as a systemic opioid-sparing technique. The most frequently investigated dose of intrathecal morphine was 100 µg (7,8).

Materials and methods

This retrospective study was conducted in University Hospital Centre Zagreb, Department of Orthopaedic surgery and Department of Anaesthesiology, ICU and pain therapy. In this study, the difference between the use of standard methods of analgesia, which include systemic administration of opioid and non-opioid analgesics, and the administration of intrathecal morphine in patients after total hip arthroplasty was examined. 100 patients were included in the research, who, due to primary coxarthrosis, were scheduled to have a total hip replacement. After the patients have been given an indication for the planned operation by the orthopaedist, all patients were examined in the anaesthesiology outpatient 3-4 weeks before the planned admission to the hospital. In the department of anaesthesiology, all patients were clinically examined, laboratory findings were accessed, and the patient's history was taken with regard to cardiorespiratory, kidney and liver diseases. Preoperative laboratory findings were in the referent range for all patients. Upon admission to the hospital, based on clinical status, laboratory and anamnestic data, patients were classified according to the American Society of Anaesthesiologists (ASA) classification into one of the IV groups. The research included patients of ASA status I, II and III. Exclusion criteria were allergy to morphine preparations, history of respiratory depression and history of nausea, vomiting after opioid administration and ASA status IV. All patients signed consent to participate in the study.
The patients who met the research criteria were grouped into one of the two examined patient groups. One group of patients received a systemic combination of opioid and non-opioid analgesics as part of postoperative analgesia, and the other group received morphine intrathecally, as well as standard therapy based on the patient's needs. The preparation of all patients who are planned to have a primary hip endoprosthesis was the same, regarding premedication, antibacterial prophylaxis and thromboprophylaxis. Patients were divided in 2 groups: test group and control group in total 100 patients. In the test group, 27 patients have received 200 µg of morphine, and 20 patients have received 250 µg. In the examined group intrathecal morphine was administered. That is an invasive procedure and involves the administration of the drug into the subarachnoid space by inserting an atraumatic sterile spinal needle. The application was part of the same procedure that applies spinal anaesthesia, only morphine was added to the local anaesthetic which was 0.5% Chirocaine (Levobupivacaine, Abbott), which was performed with atraumatic spinal needles (Becton Dickinson). During the first 24 postoperative hours the VAS scale was monitored (0-no pain, 10-the strongest possible pain). In cases where the VAS score was greater than 4, the patients received additional analgesic therapy intravenously. The pain scale was recorded for a total of 24 hours. There were 10 measurements in total. Student`s t test was used for statistics.

Results

Average VAS score per patient was collected in 24 postoperative hours. The results were compared in the test group and control group. In the test group there were in total 47 patients, while in the control group there were in total 53 patients. The patients in the test group were later divided in 2 subgroups and among them 27 patients have received 200 µg morphine while 20 have received 250 µg. The results have shown that the average VAS

score per patient per hour (during 24 postoperative hours) in the group who have received 200 µg morphine was 1,09 and in the other group who have received 250 µg was 0,64. The VAS score in the control group was 2,39. The results suggest that the least pain was felt by patients in the group who have received 250 µg. The p-value in the 250 µg group was 0.001 compared to the control group (Figure 1).

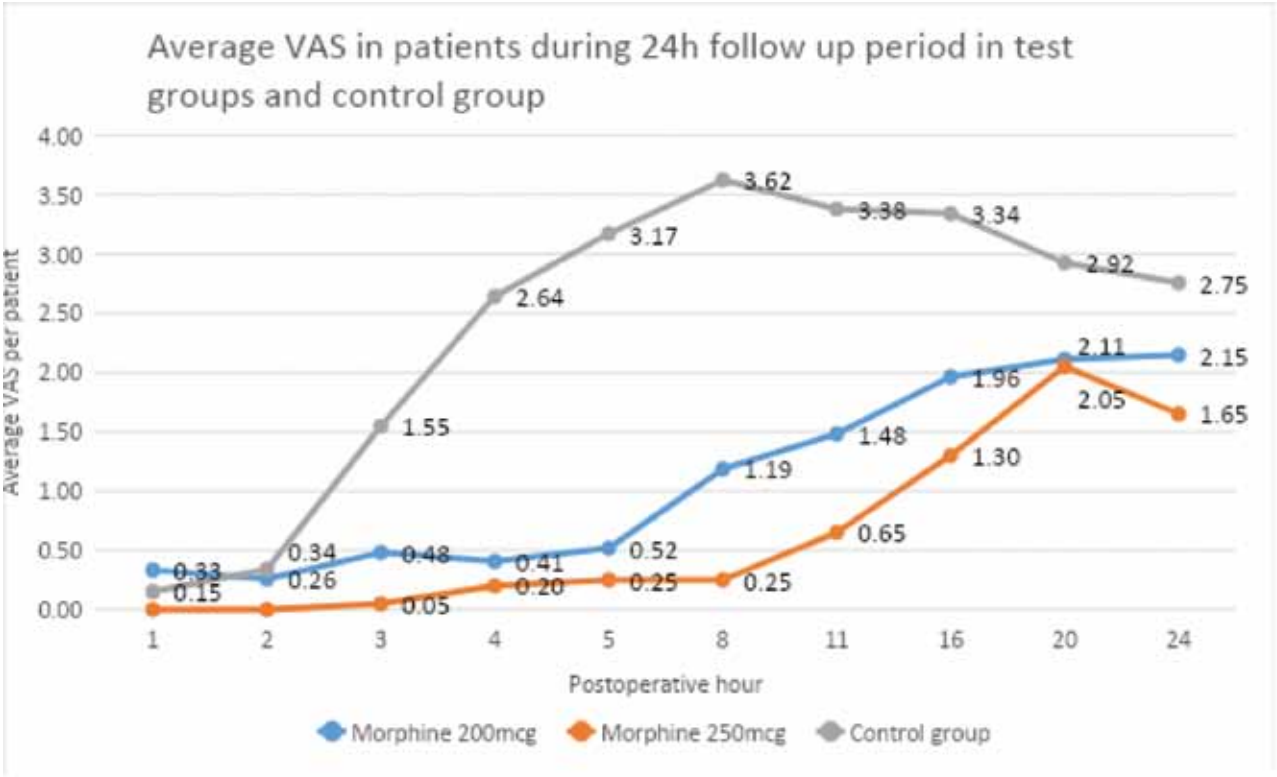


Figure 1. Comparison of average VAS scale in both test (n=47) and control group (n=53)

Discussion

The first intrathecal injection of morphine was performed in 1979 to achieve pain relief (2), and since then, this intervention has been successfully used in many surgical operations including lower limb arthroplasty (3). While hip arthroplasty is performed on almost daily basis with a short hospital stay, anaesthesiologists still hesitate to administer intrathecal morphine despite its expected analgesic effect, partially for fear of potential side-effects, especially postoperative nausea, and vomiting (PONV) and eventual respiratory depression (4). The results of meta-analysis (5) that was published in 2022 including 29 trials with 1814 patients have concluded that dose of 100 mcg is 'ceiling 'dose for analgesia and a threshold dose for increased rate of postoperative nausea and vomiting. Many studies have used intrathecal morphine doses that ranged from 35 µg (6) to 500 µg (7), while the most frequently investigated dose was 100 µg (8,9). They recommend an intrathecal dose of 100 µg for improving patient comfort without increasing the risk of PONV. One area worthy of discussion is the risk of postoperative hypoventilation. Even more if patients demonstrated a greater degree of sedation in the intrathecal morphine group, there was no effect on the rates of hypoxaemia or respiratory depression. This is important, as many physicians believe that continuous monitoring is necessary, following recommendations from the American Society of Anaesthesiologists (10).

While respiratory depression might have been a clinical problem within intrathecal morphine doses of 250 µg, as reported in the late 1980s (11), recent evidence highlights the absence of respira-

tory depression with doses below 150 µg (12), even in older people undergoing hip arthroplasty. Thus, an intrathecal morphine dose of 100 µg for lower limb arthroplasty seems to warrant no more than standard postoperative care. Notably, the duration of effect of intrathecal morphine is estimated to be up to 16 h (13) which may be the underlying reason for clinically unimportant differences in analgesic outcomes at 24 hr. However, intrathecal morphine was associated with an increased risk of PONV, worse pruritus and more urinary retention, but without impact on hospital length of stay. Therefore, these above-mentioned analyses concluded that there was a dose threshold of 100 µg, above which the rate of PONV statistically increased, with an absolute risk of 12% (5). With all said, they finally recommend an intrathecal dose of 100 mcg for improving patient comfort without increasing the risk of PONV. In our study, we have decided to administer doses between 200 µg and 250 µg because lower doses have shown to have less analgesic effect. VAS score was lower in the test group in comparison to the control group. To compare with research done by Sibanyoni et al (14), they have administered doses of 150 µg and had average VAS scale score of 1, while in our test group of 250 µg average VAS scale score was 0.64 vs 1,09 in the group who have received 200 µg. We have not encountered adverse effects such as respiratory depression, hypoventilation, urinary retention, and PONV incidence was 13% while meta-analysis (5) had shown PONV incidence of 12% when 100 µg dose administered.

Conclusion

In spite of recommendations of above-mentioned meta-analysis (4), we have decided to conduct the study based on doses higher than 100 µg due to better pain reduction. We have not encountered respiratory depression or any similar hypoventilation problems, and it is worth mentioning that PONV was noted in 13% patients who have received doses of 200 µg or 250 µg. In conclusion, patients who have received intrathecal morphine of 200 µg or 250 µg had lower pain scores compared to previously reported results with lower morphine dose. Also, patients who were administered intrathecal morphine had VAS scores lower than those in the test group. Nevertheless, this topic required further randomised control trials to prove the efficacy of intrathecal morphine in different dosing regimens.

Acknowledgements

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

References

1. Gonvers E, El-Boghdadly K, Grape S, Albrecht E. Efficacy and safety of intrathecal morphine for analgesia after lower joint arthroplasty: a systematic review and meta-analysis with meta-regression and trial sequential analysis. Anaesthesia. 2021 Dec;76(12):1648-1658.
2. Wang JK, Nauss LA, Thomas JE. Pain relief by intrathecally applied morphine in man. Anesthesiology 1979; 50: 149–51.
3. Albrecht E, Morfey D, Chan V, et al. Single-injection or continuous femoral nerve block for total knee arthroplasty? Clinical Orthopaedics and Related Research 2014; 472: 1384–93.
4. V. Maheshwari, Y.C. Blum, L. Shekhar, A.S. Ranawat, C.S. Ranawat Multimodal pain management after total hip and knee arthroplasty at the Ranawat Orthopaedic Center Clin. Orthop. Relat. Res., 467 (6) (2009), pp. 1418-1423
5. Anaesthesia 2020; 75: 54–61. Gonvers E, El-Boghdadly K, Grape S, Albrecht E. Efficacy and safety of intrathecal morphine for analgesia after lower joint arthroplasty: a systematic review and meta-analysis with meta-regression and trial sequential analysis. Anaesthesia. 2021 Dec;76(12):1648-1658.
6. Sundarathiti P, Thammasakulsiri J, Supboon S, Sakdanuwatwong S, Piangjai M. Comparison of continuous femoral nerve block(CFNB/SA) and continuous femoral nerve block with mini-dose spinal morphine (CFNB/SAMO) for postoperative analgesia after total knee arthroplasty (TKA): a randomized controlled study. BMC Anesthesiology 2015;16:38.
7. Drakeford MK, Pettine AK, Brookshire L, Ebert F. Spinal-narcotics for postoperative analgesia in total joint arthroplasty. A prospective study. Journal of Bone and Joint
8. Albrecht E, Bayon V, Hirotsu C, Al Ja'bari A, Heinzer R. Intrathecal morphine and sleep apnoea severity in patients

undergoing hip arthroplasty: a randomised, controlled, triple-blinded trial. British Journal of Anaesthesia2020;125: 811–7
9. Biswas A, Perlas A, Ghosh M, et al. Relative contributions ofadductor canal block and intrathecal morphine to analgesiaand functional recovery after total knee arthroplasty: arandomized controlled trial. Regional Anesthesia and PainMedicine2018;43: 154–60.
10. Practice Guidelines for the prevention, detection, andmanagement of respiratory depression associated withneuraxial opioid administration: an updated report by theAmerican Society of Anesthesiologists Task Force on neuraxialopioids and the American Society of Regional Anesthesia and Pain Medicine. Anesthesiology 2016;124: 535–52
11. Jacobson L, Chabal C, Brody MC. A dose-response study ofintrathecal morphine: efficacy, duration, optimal dose, and sideeffects. Anesthesia and Analgesia1988;67: 1082–8
12. Crowgey TR, Dominguez JE, Peterson-Layne C, Allen TK, MuirHA, Habib AS. A retrospective assessment of the incidence ofrespiratory depression after neuraxial morphine administrationfor postcesarean delivery analgesia. Anesthesia and Analgesia2013;117: 1368–7
13. Saldman L, Cousins M, Mather L. Intrathecal and epiduraladministration of opioids.Anesthesiology1984;61: 276–310
14. Sibanyoni, M., Biyase, N. & Motshabi Chakane, P. The use of intrathecal morphine for acute postoperative pain in lower limb arthroplasty surgery: a survey of practice at an academic hospital. J Orthop Surg Res 17, 323 (2022).

Functional Magnetic Stimulation of the Pelvis and Urinary Incontinence after Radical Prostatectomy

Tvrtko Hudolin[1], Ilija Jurić[1], Jerko Anđelić[1], Helena Kolar Mitrović[2], Tomislav Kuliš[1], Luka Penezić[1], Mirko Bakula[1], Toni Zekulić[1], Porin Perić[2], Željko Kaštelan[1]

[1] Department of Urology, Clinical Hospital Center, Zagreb, Kišpatićeva 12, 10 000 Zagreb, Hrvatska
[2] Department of Rheumatology and rehabilitation, Clinical Hospital Center, Kišpatićeva 12, 10 000 Zagreb, Hrvatska

Abstract:

Functional magnetic stimulation (FMS) is a method based on the use of a magnetic field to stimulate different parts of the body with the aim of their treatment or rehabilitation. As a noninvasive, relatively cheap and fast method without significant side effects, it is used for several decades for many parts of human body to reduce related pain or increase its functionality. In urology it is mainly indicated for pelvic floor rehabilitation to reduce problems with urination mostly in female patients, alone or more often in combination with different methods for pelvic floor rehabilitation. In this review we will present current role of FMS in patients with urinary incontinence after radical prostatectomy.

Keywords: functional magnetic stimulation, urinary incontinence, radical prostatectomy

Sažetak:

Funkcionalna magnetska stimulacija zdjelice i urinarna inkontinencija nakon radikalne prostatektomije

Funkcionalna magnetna stimulacija (FMS) je metoda koja koristi magnetno polje kako bi stimulirala različite dijelove tijela s ciljem njihova liječenja ili rehabilitacije. FMS je neinvazivna, relativno jeftina i brza metoda bez značajnih nuspojava koja se koristi više desetljeća za smanjenje bolova u različitim dijelovima tijela te povećanju njegove funkcionalnosti. U urologiji se koristi kod rehabilitacije zdjeličnog dna s ciljem smanjenja tegoba mokrenja većinom kod žena, sama ili češće u kombinaciji s drugim metodama rehabilitacije zdjeličnog dna. U ovom radu prikazati ćemo trenutnu ulogu FMS kod bolesnika s urinarnom inkontinencijom nakon radikalne prostatektomije.

Ključne riječi: funkcionalna magnetna stimulacija, urinarna inkontinencija, radikalna prostatektomija

OPEN ACCESS

Correspondence:
Tvrtko Hudolin
tvrtkohudolin@gmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 23 April 2023
Accepted: 28 May 2023
Published: 26 June 2023

Citation:
Hudolin T, Jurić I, Anđelić J, Kolar Mitrović H, Kuliš T, Penezić L, Bakula M, Zekulić T, Perić P, Kaštelan Ž. Functional Magnetic Stimulation of the Pelvis and Urinary Incontinence after Radical Prostatectomy and literature review. 556=62-63 (2023): 60-64
DOI: 10.21857/ydkx2code9

Introduction

Radical prostatectomy (RP) is considered the gold standard for the treatment of localized prostate cancer (PCa) in patients who are in good general condition and have a longer life expectancy. (1) However, this operation carries a significant risk of unwanted postoperative side effects such as erectile dysfunction (ED) and urinary incontinence (UI), which can be present in different extents (from very mild to very pronounced) and duration (from several weeks or months, up to several years and even more) in a significant number of patients. In the last two decades there has been an important progress in the diagnostic and surgical treatment of PCa, primarily towards earlier detection of the disease, but also increasingly widespread use of minimally invasive treatment modalities, all of which should reduce the frequency and intensity of these side effects, but they are still present in a relatively big number of patients. ED and IU carry a significant negative impact on the patient's quality of life and his satisfaction with the operation and present the burden to the healthcare system in general. Therefore, the emphasis is on methods that would prevent or reduce the probability of their occurrence, but also their severity and duration if they do occur.

Functional magnetic stimulation (FMS) is in use for several decades to treat many diseases, that is, to alleviate their symptoms and complaints. In urology, it is mostly used in the treatment of female incontinence by stimulating pelvic floor muscles but also having positive effect on bladder in general. (2)

The pelvic floor is a complex structure made of muscles and connective tissues, which plays a crucial role in maintaining urinary and bowel continence and normal sexual function by enabling a proper support of pelvic organs which, if insufficient, can present with different problems. Mechanism of FMS involves the application of magnetic fields to specific areas of the body to induce electrical currents within the targeted tissues. The principle behind FMS lies in Faraday's law of electromagnetic induction, where a changing magnetic field induces an electric field. (2,3) In the case of pelvic floor stimulation, FMS devices generate magnetic pulses that penetrate the pelvic region, stimulating the nerves and muscles responsible for pelvic floor function. (4,5) By stimulating the pelvic floor muscles, FMS aims to enhance muscle strength, improve coordination, and promote neuromuscular reeducation. Studies have proven benefits of using FMS for pelvic floor disorders such as stress urinary incontinence, overactive bladder, and pelvic pain syndromes. (6) Furthermore, the role of FMS in sexual dysfunction, including ED and female sexual arousal has been explored as a potential therapeutic modality to improve sexual function by enhancing pelvic floor muscle tone and increasing blood flow to the genital area with promising initial results which demand further investigation/confirmation. (7) FMS is most often performed as an outpatient procedure, where patients come for a certain number of cycles (several times a week for several weeks), according to pre-planned protocols with certain magnetic field strengths and duration of stimulation, often predefined by the FMS device manufacturers. The method is well tolerated with minimal side effects, which also ranks it among the first methods used in urinary incontinence, especially for patients who prefer non-invasive approaches. Furthermore, FMS can be used in combination with different behavioral therapy for management of incontinence, from lifestyle changes (maintaining healthy bladder habits, moderate liquid and beverage intake, monitor diet and medications, maintain bowel regularity and healthy weight as well as stop smoking) to bladder training and urgency reduction strategies, pelvic floor muscle training (without or with biofeedback), different drugs and stimulators, further improving it applicability. (8)

Urinary continence after RP

There are at least several reasons why urinary continence can be damaged after RP. Bladder, bladder neck and urethra with the prostate, as well as surrounding and belonging musculoskeletal and nervous structures and tissue form a unique functional unit that enables filling and controlled emptying of the bladder. It is known that with the years of life, i.e. aging, due to various reasons, this function is less or more impaired, therefore many of patients are "entering" surgery with already changed urinary function. (9) A large number of them have other diseases from cardiovascular and neurological to metabolic, moreover many of them have combination of these conditions, further increasing the likelihood of UI, i.e. problems with urination, after RP. When preoperative urinary function was assessed to evaluate baseline urinary status of patients, studies reported that from 10% up to almost 50% of participants have reported different forms of urinary disfunction from urinary leakage (incontinence) to obstructive urinary symptoms with different expression (from mild to severe) levels. (10-13)

Beside general factors, there are also local factors which can influence postprostatectomy continence, and among them urethral length, neurovascular bundle (NVB) status and surgical techniques are considered to be the most important one. Previous studies have shown that urethral status is an important factor for postprostatectomy UI. In order to properly assess it, different methods can be used from magnetic resonance imaging to obtain anatomical data and urodynamic studies to add functional information's regarding pressure values before and/or after the surgery.(14,15) However, these methods can add additional costs, time and burden for the patients and therefore are not used often. With the introduction of minimally invasive procedures, we have new methods which can be used to assess preserved part of the urethra by using semi-quantitatively measured on a video screen which have confirmed that patients with longer preserved urethral length have a significantly higher rate of post-operative urinary continence recovery. (16) This noninvasive approach

can be interesting for application since it can be easily done, although additional validation is needed.

NVB is a delicate structure that is located on peripheral sides of the prostate. It was initially described by the P.C. Walsh and P. Donker with pioneering work performed by dissection on a stillborn male infant to map the nerves to the bladder. In April 26, 1982, Walsh performed the first intentional nerve-sparing radical prostatectomy on a 52-year-old professor of management. It took several months for the patient to make a full recovery, but he has remained fully functional and cancer-free ever since. (17) Since this initial description, numerous papers have been published about NVB and its role in preservation of erectile and urinary function, and although its role in preserving erection is proven, conclusions regarding its role in urinary continence are not so straight forward. There are several issues that need to be resolved before a final conclusion is reached, which may also not be universally applicable to all patients. For example, how important are nerves passing through NVB for continence itself? If we preserve them, will our patients for sure be continent and when? Shortly after surgery, i.e. catheter removal, or several days, week or months after surgery? Is anatomical preservation also functional? Is NVB preservation just a marker of less invasive procedure and thus less damage to the urethral/periurethral tissue, which is then actually the real cause of better continence after nerve sparing RP? It is not easy to answers these questions, and in search of an answer in the published literature, we should also critically analyze the studies since they can differ significantly in their design including the number of patients and their characteristics (age, body mass index, comorbidities, etc.), procedures performed (open, laparoscopic or robotic RP), scoring of postoperative continence and potence as well as patient follow up, but in general we can say that there has been shown that preservation of NVB has a positive effect on postprostatectomy continence at least for early postoperative period.(13)

Surgical experience and the technique is something that has also been shown to be very important for preservation of urinary continence and erectile function but also for achieving cancer free status. After all it is logical that with more experience, we can perform better surgery. Numerous papers have been published about surgical technique, furthermore, afore mentioned preservation of urethral length and NVB sparing technique are also parts of the surgical approach. These methods as bladder neck sparing technique, Retzius sparing technique, dorsal venous complex resection/ligation, posterior reconstruction (Rocco Stitch), anterior

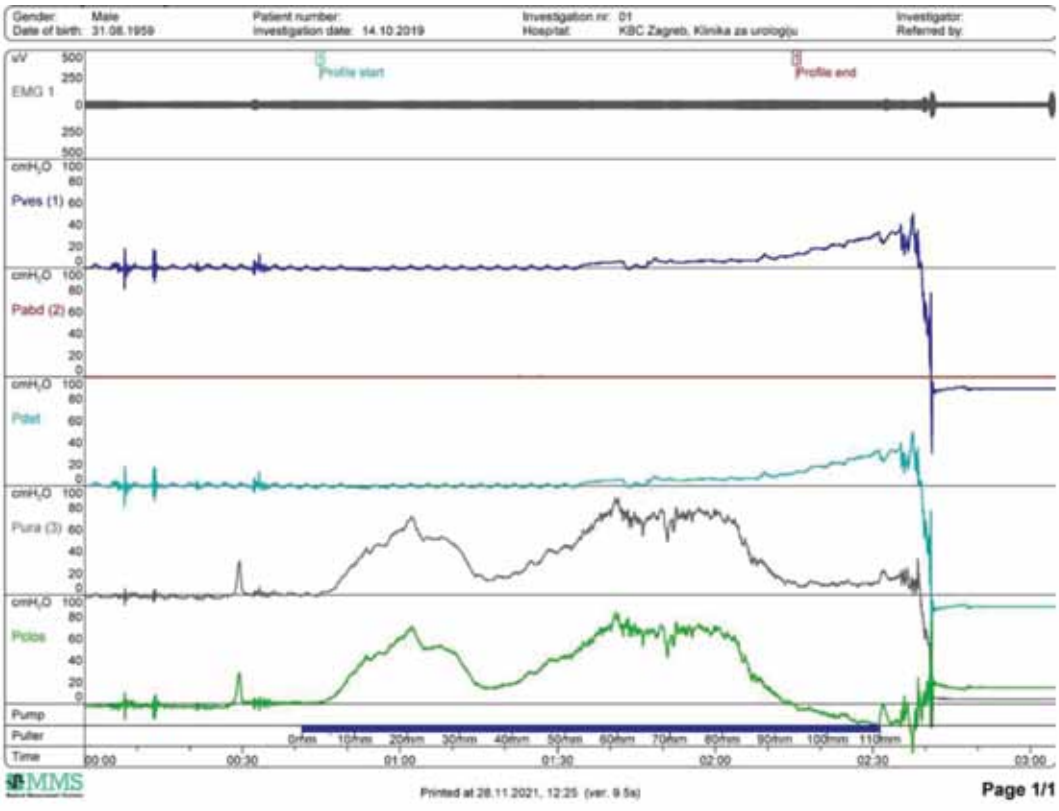


Figure 1. Image of profilometric measurement of the functional urethra before RP.

retropubic suspension (Patel Stitch), total anatomical reconstruction, placement of suprapubic tube, just to mention most common, have introduced smaller or bigger changes in surgical procedures, to increase continence rates.(18) If we have so many procedures and modification used by different surgeons than we do not have a standard procedure and it is logical that our results can be different. A number of factors influence the type of surgery, and the steps involved, from our education and personal preferences to patient characteristics and technical capabilities and will likely always differ or be somewhat different for different surgeons. Therefore, it is even more important to have a standard procedure which can be used after surgery or even before to improve urinary continence after RP.

The number of studies that investigated the role of FMS in patients after PR is not large and mostly involved a relatively small number of patients, so their results are limited, although in principle a positive effect of FMS has been proven.(19,20) The improvement itself was manifested by shortening the time to achieve urinary continence, after FMS, i.e. by reducing the number of pads used, but also by increased patient satisfaction after therapy. (21-24)

In order to obtain additional information about the role of FMS after RP, we are conducting a clinical trial using the electromagnetic generator of the Tesla Care device (IskraMedical d.o.o. Ljubljana Slovenia) which has already been used in our institution since 2018, mainly for female stress incontinence. Patients will be randomized in two groups, those treated with FMS from the electromagnetic generator under the seat and the group without contact between the electromagnetic generator and the pelvis (sham treatment). Patients will have two weekly treatments as an outpatient procedure for 4 weeks for a total of 8 treatments according to a predefined protocol by the manufacturer with additional modifications if needed (Figure 2). For urinary continence assessment we will use the International Consultation on Incontinence Questionnaire (ICIQ-UI SF) questionnaire as well as findings about the number of pads used/day, both procedures have been validated and are widely used as simple, fast and objective methods for the assessment of urinary function. For statistical analysis we will use the program STATISTICA 6.1 StatSort Inc., Tulsa, OK, USA. The patients will be followed for at least one year after RP. This trial will provide additional information about on the role of FMS in patients after RP that can be used to further improve our knowledge of the role of FMS in urinary incontinence.

Figure 2. FMS of the pelvic floor after RP (patient position and stimulator settings).

References

1) Heidenreich A, Aus G, Bolla M, Joniau S, Mateev VB, Schmid HP. EAU Guidelines on prostate cancer. Eur Urol. 2008;53:68-80.
2) Galloway NTM, El-Galley RE, Sand PK, Appell RA, Russell HW, Carlan SJ. Extracorporeal magnetic innervation therapy for stress urinary incontinence. Urology. 1999;53:1108-11.
3) Barker AT, Freeston IL, Jalinous R, Jarratt JA. Magnetic stimulation of the human brain and peripheral nervous system: An introduction and the results of an initial clinical evaluation. Neurosurgery. 1987;20:100-109.
4) Lim R, Lee SWH, Tan PY, Liong ML, Yuen KH. Efficacy of electromagnetic therapy for urinary incontinence: A systematic review. Neurourol. Urodyn. 2014;34:713-22.
5) Stewart F, Berghmans B, Bø K, Glazener CM. Electrical stimulation with non-implanted devices for stress urinary incontinence in women. Cochrane Database Syst. Rev. 2017;12:CD012390.
6) Lukanović D, Kunič T, Batkoska M, Matjašič M, Barbič M. Effectiveness of Magnetic Stimulation in the Treatment of Urinary Incontinence: A Systematic Review and Results of Our Study. J Clin Med. 2021;10:5210.
7) Rosenbaum TY, Owens A. The role of pelvic floor physical therapy in the treatment of pelvic and genital pain-related sexual dysfunction (CME). J Sex Med. 2008;5:513-23.
8) Newman DK and Wein AJ. Office-Based Behavioral Therapy for Management of Incontinence and Other Pelvic Disorders. Urol Clin N Am. 2013;40:613-635.
9) Stanford JL, Feng Z, Hamilton AS, Gilliland FD, Stephenson RA, Eley JW, et al. Urinary and sexual function after radical prostatectomy for clinically localized prostate cancer: the Prostate Cancer Outcomes Study. JAMA. 2000;283:354-60.
10) Potosky AL, Legler J, Albertsen PC, Stanford JL, Gilliland FD, Hamilton AS, et al. Health outcomes after prostatectomy or radiotherapy for prostate cancer: results from the Prostate Cancer Outcomes Study. J Natl Cancer Inst. 2000;92:1582-92.
11) Salonia A, Lanzi R, Scavini M, Pontillo M, Gatti E, Petrella G, et al. Sexual function and endocrine profile in fertile women with type 1 diabetes. Diabetes Care. 2006;29:312-6.
12) Ficarra V, Novara G, Mottrie A, Wilson TG, Zattoni F, Montorsi F. Reply to Michael Froehner and Manfred P. Wirth's letter to the editor re: Vincenzo Ficarra, Giacomo Novara, Raymond C. Rosen, et al. systematic review and meta-analysis of studies reporting urinary continence recovery after robot-assisted radical prostatectomy. Eur Urol 2012;62:405-17. Eur Urol. 2013;63:e39-40.
13) Steineck G, Bjartell A, Hugosson J, Axén E, Carlsson S, Stranne J, et al. LAPPRO steering committee. Degree of preservation of the neurovascular bundles during radical prostatectomy and urinary continence 1 year after surgery. Eur Urol. 2015;67:559-68. doi: 10.1016/j.eururo.2014.10.011. Epub 2014 Oct 28. PMID: 25457018.
14) Hoyland K, Vasdev N, Abrof A, Boustead G. Post-radical prostatectomy incontinence: etiology and prevention. Rev Urol. 2014;16:181-8. PMID: 25548545; PMCID: PMC4274175.
15) Bakula M, Hudolin T, Kolar Mitrovic H, Kastelan Z. Urethral pressure profile before radical prostatectomy as a predictor of early postoperative continence. Neurourol Urodyn. 2022;41:1431-9.
16) Ando S. Longer preserved urethral length in robot-assisted radical prostatectomy significantly contributes to post-operative urinary continence recovery. BJUI Compass 2021;3:184-90. doi: 10.1002/bco2.128. eCollection 2022 Mar.
17) Walsh PC, Donker PJ. Impotence following radical prostatectomy: insight into etiology and prevention. J Urol. 1982;128:492-7.
18) Urkmez A, Ranasinghe W and Davis JW. Surgical techniques to improve continence recovery after roboti-assisted radical prostatectomy. Translation Andrology and Urology 2020;9:3036-48.
19) Chang PC, Wu CT, Huang ST, Chen Y, Huang HC, Hsu YC et al. Extracorporeal magnetic innervation increases functional bladder capacity and quality of life in patients with urinary incontinence after robotic-assisted radical prostatectomy. Urological Science 2015;26:250-3.
20) Koo D, So SM Lim JS. Effect of extracorporeal magnetic innervation (ExMI) pelvic floor therapy on urinary incontinence after radical prostatectomy. Korean J Urol. 2009;50:23-7.
21) Yamanishi T, Yasuda K, Suda S, Ishikawa N, Sakakibara R and Hattori T. Effect of functional continuous magnetic stimulation for urinary incontinence. J Urol 2000;163:456-9.
22) Fujishiro T, Enomoto H, Ugawa Y, Takahashi S, Ueno S and Kitamura T. Magnetic stimulation of the sacral roots for the treatment of stress incontinence: an investigetional study and placebo controlled trial. J Urol 2000; 164:1277-9.
23) Chandi DD, Groenendijk PM, Venema PL. Functional extracorporeal magnetic stimulation as a treatment for female urinary incontinence: 'the chair'. BJU Int 2004;93:539-42.
24) Almeida FG, Bruschini H, Srougi M. Urodynamic and clinical evaluation of 91 female patients with urinary incontinence treated with perineal magnetic stimulation: 1-year follow-up. J Urol 2004;171:1571-5.

Lifestyle medicine – a new promise for shifting the tide of non-communicable diseases

Ivana Kolčić[1,2]

[1] Department of Public Health, University of Split School of Medicine, Soltanska 2, 21000 Split, Croatia
[2] Algebra LAB, Algebra University College, Gradišćanska ul. 24, 10000 Zagreb, Croatia

Abstract:

Lifestyle medicine developed as a response to the global burden and consequences of non-communicable diseases (NCDs), which dominate epidemiological trends in mortality, morbidity, and disability worldwide during the last couple of decades. Lifestyle medicine includes six pillars, the use of whole food, plant-predominant dietary pattern, regular physical activity, restorative sleep, stress management, avoidance of risky substances, and positive social connection, as evidence-based and primary therapy modalities aiming for treatment and reversal of chronic diseases. Interest in lifestyle medicine is increasing globally, and it was even further advanced during the COVID-19 pandemic. Additionally, professional interest in lifestyle medicine is fueled by the extended learning opportunities based on the findings of recent studies demonstrating the reversible nature of NCDs, especially for diabetes type 2 and obesity. These results request a thorough contemplation of our current understanding of the "uncurable" nature of diabetes type 2, but also for other chronic non-communicable diseases, and demand a paradigm shift in medical practice and education. This requires education of medical students and doctors, adaptation of reimbursement and health insurance policies, and forming multidisciplinary teams that will be able to deliver lifestyle intervention procedure to all who need it. The future of healthcare and NCDs management is the long-term self-care by patients, assisted by physicians and other professionals, such as nurses, nutritionists, physical therapists or kinesiologists, psychologists, health educators, pharmacists, and social workers, as indicated. The ultimate goal has to be reaching the best possible health in individuals and communities. The time for action is yesterday.

Keywords: lifestyle medicine, non-communicable diseases, disease remission, nutrition, diabetes mellitus type 2

Sažetak:

Lifestyle medicina – novo obećanje za promjenu plime nezaraznih bolesti

Medicina životnog stila razvila se kao odgovor na globalno opterećenje i posljedice kroničnih nezaraznih bolesti, koje dominiraju epidemiološkim trendovima u mortalitetu, morbiditetu i onesposobljenosti diljem svijeta tijekom posljednjih nekoliko desetljeća. Medicina životnog stila uključuje šest stupova; korištenje cjelovite hrane, tj. obrazac prehrane u kojem prevladavaju namirnice biljnog podrijetla, redovitu tjelesnu aktivnost, obnavljajući san, upravljanje stresom, izbjegavanje rizičnih tvari i pozitivnu društvenu povezanost, kao primarne terapijske modalitete utemeljene na dokazima, s konačnim ciljem liječenja i remisije kronične bolesti. Interes za medicinu životnog stila je u porastu na

OPEN ACCESS

Correspondence:
Ivana Kolčić
ikolcic@mefst.hr

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 15 May 2023
Accepted: 01 June 2023
Published: 26 June 2023

Citation:
Kolčić I. Lifestyle medicine – a new promise for shifting the tide of non-communicable diseases 556=62-63 (2023): 66-70
DOI: 10.21857/m16wjcnz59

globalnoj razini, a još je više uznapredovao tijekom COVID-19 pandemije. Uz to, interes profesionalaca je potaknut i proširenim mogućnostima obrazovanja temeljem rezultata nedavnih studija, koje pokazuju reverzibilnu prirodu kroničnih nezaraznih bolesti, posebice za dijabetes tipa 2 i pretilost. Ovi rezultati zahtijevaju temeljito razmatranje našeg trenutnog razumijevanja "neizlječive" prirode dijabetesa tipa 2, ali i drugih kroničnih nezaraznih bolesti te zahtijevaju promjenu paradigme u medicinskoj praksi i obrazovanju. Za to je potrebna edukacija studenata medicine i liječnika, prilagodba zdravstvene politike i zdravstvenog osiguranja te formiranje multidisciplinarnih timova, koji će biti osposobljeni provesti proceduru promjene životnog stila za sve kojima je to potrebno. Budućnost zdravstvene skrbi i upravljanja kroničnim bolestima je dugoročno samozbrinjavanje pacijenata, uz pomoć liječnika i drugih stručnjaka, kao što su medicinske sestre, nutricionisti, fizikalni terapeuti ili kineziolozi, psiholozi, zdravstveni edukatori, farmaceuti i socijalni radnici, prema indikacijama. Krajnji cilj mora biti postizanje najboljeg mogućeg zdravlja pojedinaca i zajednice. Vrijeme za akciju je jučer.

Ključne riječi: medicina životnog stila, kronične nezarazne bolesti, remisija bolesti, prehrana, dijabetes tipa 2

Introduction

During the past couple of decades, non-communicable diseases (NCDs) have dominated epidemiological trends and statistics in mortality, morbidity, and disability worldwide. For example, ischemic heart disease and stroke have been the second and third global leading cause of disability-adjusted life-years (DALYs) in 2019, estimated to have risen overall by 50.4% and 32.4% from 1990 to 2019, respectively (1). But, the most alarming increase was recorded for diabetes, with a global rise of 147.9% during the last three decades (1). These and other non-communicable diseases are driven mostly by lifestyle-related risk factors. Daily habits and lifestyle patterns, including smoking, unhealthy dietary practices, and lack of physical activity all contribute to these statistics. For instance, in 2019, the leading risk factor for death globally was high systolic blood pressure (accounting for estimated 19.2% or 10.8 million deaths), followed by all types of tobacco exposure, which accounted for 8.71 million deaths or 15.4% (2). Additionally, exposures and risk factors that are particularly worrisome on the global scale due to their continuous and further increase (estimated to be increasing >0.5% per year) include alcohol use, drug use, high fasting plasma glucose, high systolic blood pressure, and high BMI, while the exposure to metabolic risks increased by 1.37% per year from 1990 to 2019 (2).

The extreme results on cardiometabolic health were obtained from the National Health and Nutrition Examination Survey 2009-2016 in the USA, where only 12.2% of adults were found to be metabolically healthy (3). Not very surprisingly, optimal metabolic health, defined as having optimal levels of waist circumference, glucose, blood pressure, HDL cholesterol, and not taking any related medication, was more commonly found in women, younger adults, more educated people, as well in those who were never smoking, were practicing vigorous physical activity, and had low BMI (3). Contrary to the common belief that lean people are usually healthy, this study found that only less than one-third of normal-weight adults were metabolically healthy in the USA (3).

One of the biggest and far-reaching rupture of the modern era worldwide, COVID-19 pandemic, found this poor overall population health as a fruitful ground for sowing death and terror. For instance, 63.5% of COVID-19 hospitalizations until November 18, 2020 in US adults were attributable to four cardiometabolic conditions; 30.2% were attributable to obesity, 26.2% to hypertension, 20.5% to diabetes, and 11.7% to heart failure (4). As the editorial in The Lancet Diabetes & Endocrinology concluded, "COVID-19 has sent the world a wake-up call about its inaction on metabolic diseases; in the post-COVID-19 era, metabolic health must be a priority, with obesity taking center stage as the number one non-communicable public health concern of our time" (5).

Aforementioned and so many more similar epidemiologic data, alongside the monetary costs and immeasurable loss in productivity and well-being associated with the current health picture of the global population, point to the deep crisis in health we have been facing for some time now. We need urgent effective and robust solutions for tackling non-communicable diseases and preventing further degradation of human potential. One such promising solution is Lifestyle Medicine.

Definition and Development of Lifestyle Medicine

Given the complex nature of chronic diseases, their strong causation in daily habits, choices and lifestyle, and their enormous

global burden, a new way of thinking started to emerge. The term "lifestyle medicine" first appeared more than 30 years ago, coined by Ernst Wynder, American epidemiologist, who mentioned it for the first time at a congress held in Brussels in 1989 (6). James Rippe edited the first book describing this emerging field of medicine in 1999, and the first professional society for physicians was founded in the USA, called the American College of Lifestyle Medicine. Today this is a regulated new medical field, with its own global certification program that was introduced in 2016 in order to standardize the field (6). Lifestyle medicine is even on its way of becoming a new specialty (7). Interest in lifestyle medicine is global and increasing, and it was especially advanced during disruptions from the COVID-19 pandemic, but also due to the expanded educational opportunities in the field, and a changing healthcare landscape (8), which demands an adjusted approach to NCDs.

The current definition of lifestyle medicine states that it is "a medical specialty that uses therapeutic lifestyle interventions as a primary modality to treat chronic conditions including, but not limited to, cardiovascular diseases, type 2 diabetes, and obesity. Lifestyle medicine certified clinicians are trained to apply evidence-based, whole-person, prescriptive lifestyle change to treat and, when used intensively, often reverse such conditions. Applying the six pillars of lifestyle medicine - a whole-food, plant-predominant eating pattern, physical activity, restorative sleep, stress management, avoidance of risky substances and positive social connections - also provides effective prevention for these conditions" (9).

Such holistic health care model is not at all new. For example, Hippocrates highlighted the importance of understanding the patient's health, emphasized environmental causes and natural treatments of diseases, especially nutrition and lifestyle, and the need for the "harmony between the individual and the social and natural environment" (10). In many aspects, lifestyle medicine is the "resurrection" of the teaching of Hippocrates. It places the whole patient in the center of care and it emphasizes the broader circumstances the person lives in, as depicted in inclusion of as many as the six pillars of lifestyle medicine. These pillars incorporate nutrition, physical activity, sleep, stress, addictions and risky behaviors, as well as commonly underestimated, but crucially important, social aspects and personal social interactions. Given the broad scope, the need for a multidisciplinary team is rendered in lifestyle medicine practice, including professionals of different backgrounds. These team members are invited in order to provide effective medical care within the interdisciplinary team of broader health care professionals. The core team usually consists of the physician, nurse, nutritionist, physical therapist or kinesiologist, psychologist, and if needed a health educator, a social worker and a pharmacist (6). Additionally, it is important to stress out that lifestyle medicine is not at all in opposition to indicated pharmacological and surgical treatment and procedures. Lifestyle medicine is not an alternative medicine direction, and it embraces all the technological and scientific advances modern medicine has to offer for the betterment of the patient. However, the main difference between lifestyle medicine and conventional medicine is the primary focus towards modification of lifestyle pattern and daily habits (as they are the root cause of NCDs), instead of the medicaments used as the first line of intervention. Liana Lianov and Mark Johnson proposed the initial lifestyle medicine competencies for primary care physicians in 2010, in the domains of leadership (2 competencies), knowledge (2 competencies), assessment (3 competencies), management skills (4 competencies), and office and community support (4 competencies) (11). These competencies have been updated recently, placing focus on enduring clinical knowledge and skills, but also including the knowledge of the impact of our lifestyles on planetary health, given its relevance and repercussions to our health and survival (12).

The Evidence on Association Between Lifestyle Habits and Health Outcomes

The abundance of evidence behind what Hippocrates recommended and taught regarding protection of health and disease prevention have emerged in the recent years. Many population-based studies have demonstrated and quantified the effect of healthy lifestyle on positive health outcomes. One such study from Germany, including 23,153 subjects during a mean follow-up of 7.8 years showed that four simple healthy lifestyle habits can result in 78% lower risk of developing a chronic disease (13). Namely, subjects who never smoked, and were having a BMI <30 kg/m^2, performing physical activity for ≥3.5 h per week, and were adhering to healthy dietary principles, had 93% reduced risk for developing diabetes, 81% reduced risk for developing myocardial infarction, and 36% reduced risk for developing cancer, compared to subjects who had none of the investigated healthy habits (13).

Another large population-based study from the USA (N=123,219) examined life expectancy of people at the age of 50 years, depending on the number of healthy, low-risk lifestyle factors present (14). The main findings of this study are striking. Women who had all five investigated healthy habits (never smoking, having ≥3.5 h/week of moderate to vigorous intensity physical activity, having high diet quality, moderate alcohol intake, and BMI <25 kg/m^2) could look ahead to a life expectancy of 43.1 years at age of 50 years, compared to 29.0 years of life expectancy for women who adopted none of these low-risk lifestyle factors, amounting to 14 years of extra life (14). The numbers for men were similar, with the difference of extra 12.2 years of life expectancy that could be attributed to a healthy lifestyle. This study also showed that adults with all five healthy habits had 74% reduced risk for all-cause mortality, 65% reduced risk for cancer mortality, and 82% for cardiovascular disease mortality, compared to adults with zero healthy habits during 34 years of follow-up (14).

The study that jointly analyzed data from 12 European cohorts with the mean follow-up of 12.5 years added more compelling evidence towards favorable effects of healthy lifestyle, namely towards the number of disease-free life-years in adults who adopted a healthy lifestyle, estimated according to their smoking status, BMI, physical activity, and alcohol consumption (15). This study found that men could expect 9.9 additional healthy years without chronic diseases (type 2 diabetes, coronary heart disease, stroke, cancer, asthma, and chronic obstructive pulmonary disease), while women could expect 9.4 additional healthy years associated with healthy lifestyle (15).

These studies and many more that can be found in the literature have shown the potential of healthy lifestyle for promotion and protection of good health. However, recent studies also point towards extraordinary effects of healthy lifestyle and lifestyle modification on NCDs treatment and even disease remission (reversal). One such seminal study showed that a dietary intervention can be and should be an important clinical option to consider in the treatment of moderate to severe depression (16). In this randomized controlled trial, entitled "Supporting the Modification of lifestyle In Lowered Emotional States" (SMILES), during the period of only 12 weeks, the intervention group received an improved diet using a modified Mediterranean diet model, which was hypothesized to be superior to a social support (befriending) applied in the control group, with the primary outcome of reducing the severity of depressive symptomatology. The results of this study showed that remission of depression was achieved in 32.3% of subjects from the intervention group and in 8.0% of subjects from the control group, which yielded a statistically significant result for the number needed to treat (NNT) of 4.1 (95% CI 2.3–27.8) (16). This is the first study of its kind to prove, in a rigorous experimental setting, the immense positive potential of heathy nutrition on mental health, without the risk of serious side-effects associated with antidepressant medications.

Another groundbreaking and mindset shifting study was focused on the possibility of remission of diabetes type 2 using an intensive lifestyle intervention in a primary care-led weight-management program (17). DiRECT study is a randomized controlled trial, which included middle aged subjects (20-65 years) diagnosed with type 2 diabetes less than 6 years before inclusion in the study, with BMI 27-45 kg/m^2, and without insulin treatment (17). The coprimary outcomes included weight loss of ≥15 kg, and remission of diabetes (defined as HbA1c less than 6.5%). The lifestyle intervention group procedure started with the withdrawal of antidiabetes and antihypertensive drugs, followed by total diet replacement (825-853 kcal per day formula diet for 12-20 weeks), continued with stepped food reintroduction (2-8 weeks), and finally followed by structured support for weight-loss maintenance. Control group received the best-practice care in accordance with guidelines (17). After two years of follow-up, 35.6% of subjects in the overall intervention group, and only 3.4% of subjects in the control group achieved remission of diabetes (odds ratio 25.82 [95% CI 8.25 to 80.84], p<0.0001), whereas 70% of the subjects who managed to lose ≥15 kg, and to maintain this weight loss, achieved and sustained remission of disease (17). Interestingly and surprisingly, serious adverse events were more frequently recorded in the control group than in the intervention group (17). This study is not an isolated anomaly in the literature. Very similar randomized controlled study, with similar intervention protocol and inclusion criteria, was conducted in the primary care and community settings in Qatar (18). The main results of DIADEM-I study include diabetes remission achieved in 61% of subjects in the intervention group, compared with 12% of subjects in the control group (odds ratio 12.03 [95% CI 5.17 to 28.03], p<0.0001) (18).

These results request a thorough contemplation of our current understanding of the "uncurable" nature of diabetes type 2, but also for other chronic non-communicable diseases, and demand a paradigm shift in medical practice and education.

Conclusion: Next Steps and Call for Action

The need for reducing the burden of NCDs is great and urgent. Considering the scientific evidence about the beneficial effect of healthy lifestyle for prevention of NCDs, as well as the new evidence demonstrating that NCDs can be successfully treated and even put into remission using lifestyle modifications, we need to focus urgently on the ways and opportunities to apply lifestyle medicine principles into daily clinical practice. With the advancement of technology and telemedicine, growing emphasis on home-based chronic care due to cost reduction and effectiveness, and widening adoption of personalized, patient-empowered treatments, the time is ripe for lifestyle medicine interventions to move into the mainstream of clinical care, and the time for lifestyle medicine is now (8). This requires education of medical students and doctors, adaptation of reimbursement and health insurance policies, and forming multidisciplinary teams that will be able to deliver lifestyle intervention to all who need it. This team will be able to equip the person with NCD diagnosis, as well as the person who is at increased risk for NCDs, with knowledge and tools for long-term self-care and for achieving their best possible health (6). The time for action is yesterday.

References

1. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396:1204-1222.
2. GBD 2019 Risk Factors Collaborators. Global burden of 87 risk factors in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020;396:1223-1249.
3. Araújo J, Cai J, Stevens J. Prevalence of Optimal Metabolic Health in American Adults: National Health and Nutrition Examination Survey 2009-2016. Metab Syndr Relat Disord. 2019;17:46-52.
4. O'Hearn M, Liu J, Cudhea F, Micha R, Mozaffarian D. Coronavirus Disease 2019 Hospitalizations Attributable to Cardiometabolic Conditions in the United States: A Comparative Risk Assessment Analysis. J Am Heart Assoc. 2021;10:e019259.
5. The Lancet Diabetes Endocrinology. Metabolic health: a priority for the post-pandemic era. Lancet Diabetes Endocrinol. 2021;9:189.
6. Kolčić I, Dragun T, Eds. Lifestyle Medicine: the Roadmap to Our Best Possible Health. [Internet]. Split: University of Split School of Medicine; 2021, [accessed 02.05.2023.] Available at: https://urn.nsk.hr/urn:nbn:hr:171:177363
7. Sayburn A. Lifestyle medicine: a new medical specialty? BMJ. 2018;363:k4442.
8. Collings C, Frates EP, Shurney D. The Time is Now For Lifestyle Medicine: Lesson From Lifestyle Medicine Leaders. Am J Lifestyle Med. 2022;16:557-561.
9. American College of Lifestyle Medicine. Definition of Lifestyle Medicine. [Internet]. [accessed 03.05.2023.] Available at: https://lifestylemedicine.org/overview/
10. Kleisiaris CF, Sfakianakis C, Papathanasiou IV. Health care practices in ancient Greece: The Hippocratic ideal. J Med Ethics Hist Med. 2014;7:6.
11. Lianov L, Johnson M. Physician competencies for prescribing lifestyle medicine. JAMA. 2010;304:202-3.
12. Lianov LS, Adamson K, Kelly JH, Matthews S, Palma M, Rea BL. Lifestyle Medicine Core Competencies: 2022 Update. Am J Lifestyle Med. 2022;16:734-739.
13. Ford ES, Bergmann MM, Kröger J, Schienkiewitz A, Weikert C, Boeing H. Healthy living is the best revenge: findings from the European Prospective Investigation Into Cancer and Nutrition-Potsdam study. Arch Intern Med. 2009;169:1355-62.
14. Li Y, Pan A, Wang DD, Liu X, Dhana K, Franco OH, *et al.* Impact of Healthy Lifestyle Factors on Life Expectancies in the US Population. Circulation. 2018;138:345-355.
15. Nyberg ST, Singh-Manoux A, Pentti J, Madsen IEH, Sabia S, Alfredsson L, *et al.* Association of Healthy Lifestyle With Years Lived Without Major Chronic Diseases. JAMA Intern Med. 2020;180:760-768.
16. Jacka FN, O'Neil A, Opie R, Itsiopoulos C, Cotton S, Mohebbi M, *et al.* A randomised controlled trial of dietary improvement for adults with major depression (the 'SMILES' trial). BMC Med. 2017;15:23.
17. Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, *et al.* Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 2019;7:344-355.
18. Taheri S, Zaghloul H, Chagoury O, Elhadad S, Ahmed SH, El Khatib N, *et al.* Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial. Lancet Diabetes Endocrinol. 2020;8:477-489.

Ataxia as an initial presentation of Sporadic Creutzfeld – Jakob disease : an atypical case report and literature review

Slaven Lasić[1], Iva Mihaljević[1], Nataša Katavić[2], Ivana Šušak Sporiš[1,3], Jasna Badžak[1], Petra Bago Rožanković[1,4]

[1] Department of Neurology, University Hospital Dubrava, Zagreb, Croatia
[2] Department of Radiology, University Hospital Dubrava, Zagreb, Croatia
[3] Department of Psychiatry and Neurology, Faculty of Dental Medicine and Health, JJ Strossmayer University of Osijek, Osijek, Croatia
[4] School of Medicine, Catholic University of Croatia, Zagreb, Croatia

Abstract:

Sporadic Creutzfeldt Jakob disease is a rare, fast-progressing neurodegenerative disease with a fatal outcome. Even though its treatment options are scarce, and there is no cure for the disease, adequate diagnosis can help patients and their families come to terms with the disease on time, and give them valuable time to plan accordingly. We report a case of a patient presenting to our emergency department with a 2-week history of ataxia, and oscillopsia. Her initial neurological examination revealed subtle dysarthria, diplopia with left gaze, wide-based ataxic gait with occasional small steps, sinistropulsion in the Romberg position, and ataxia of the limbs, predominantly of the left arm. The patient at that time did not exhibit cognitive impairment, movement disorders, or other neurological signs. Her initial brain MSCT was without lesions or other pathomorphological supstrate. During hospitalization, treatable causes were firstly excluded with blood and CSF lab tests excluding metabolic, toxic, infectious, autoimmune, and paraneoplastic causes. Detailed medical history revealed subtle personality changes, while cognitive testing revealed moderate cognitive impairment. Brain MRI and EEG 4 days after hospitalization reported typical changes seen with advanced prion disease surprisingly being the fact that the patient had a mild to moderate clinical picture. RtQuIC analysis of the CSF was performed to prove probable sCJD and was positive. The patient's family were given instructions, while the wishes of the patient, and family members were fulfilled concerning planning future care. Afterward, the patient's state deteriorated rapidly as per the tragic prognosis of sCJD resulting in akinetic mutism, and death. Ataxia without cognitive impairment, rigor, or movement disorders is an uncommon clinical presentation for a disease with a 1:1 000 000 incidence rate. Modern diagnostic methods in way of more advanced brain MRI capabilities, and RT-QuIC obviate the need for complicated, and potentially infectious brain biopsy in diagnosing sCJD. Alongside the case report, we present a short but comprehensive literature review of modern data regarding the sCJD. This case report and literature review serve to educate clinicians about this rare but devastating disease.

Keywords: ataxia, Creutzfeld – Jakob disease, rare disease

Sažetak:

Ataksija kao početna manifestacija sporadične Creutzfeld-Jakobove bolesti: atipični prikaz slučaja i pregled literature

Sporadična Creutzfeldt Jakobova bolest je rijetka, brzo napredujuća neurodegenerativna bolest sa smrtnim ishodom. Iako su mogućnosti liječenja oskudne, bez etiološke mogućnosti liječenja, adekvatna

OPEN ACCESS

Correspondence:
Slaven Lasić
lasicslaven1993@gmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 28 April 2023
Accepted: 01 June 2023
Published: 26 June 2023

Citation:
Lasić S, Mihaljević I, Katavić N, Šušak Sporiš I, Badžak J, Bago Rožanković. Ataxia as an initial presentation of Sporadic Creutzfeld – Jakob disease : an atypical case report and literature review. 556=62-63 (2023): 72-81
DOI: 10.21857/yrvgqtw1o9

dijagnoza može pomoći pacijentima i njihovim obiteljima da na vrijeme prihvate bolest te im dati dragocjeno vrijeme za planiranje u skladu s nepovoljnom prognozom. Predstavljamo slučaj pacijentice koja se prezentirala u našoj hitnoj službi s 2-tjednom poviješću ataksije i oscilopsije. Njezin inicijalni neurološki pregled otkrio je suptilnu dizartriju, diplopiju s lijevim pogledom, široki ataksični hod s povremenim malim koracima, sinistropulziju u Rombergovom položaju i ataksiju udova, pretežno lijeve ruke. Pacijentica u to vrijeme nije pokazivala kognitivno oštećenje, poremećaje pokreta niti druge neurološke znakove. Njezin početni MSCT mozga nije ukazivao na patomorfološki supstrat. Tijekom hospitalizacije uzroci koji se mogu liječiti najprije su isključeni laboratorijskim pretragama krvi i likvora, isključujući metaboličke, toksične, infektivne, autoimune i paraneoplastične uzroke. Detaljna povijest bolesti otkrila je suptilne promjene osobnosti, dok je kognitivno testiranje otkrilo umjereno kognitivno oštećenje. MR mozga i EEG 4 dana nakon hospitalizacije prikazali su tipične promjene uočljive kod uznapredovale prionske bolesti, što je iznenađujuća činjenica s obzirom da je pacijentica imala blagu do umjerenu kliničku sliku. Provedena je RT-QuIC analiza likvora kako bi se dokazao vjerojatni sCJD koja pristiže pozitivna. Date su upute obitelji bolesnice te su ispunjene želje bolesnice i članova obitelji oko planiranja buduće njege. Nakon hospitalizacije, stanje pacijentice se brzo pogoršalo prema tragičnoj prognozi sCJD-a te je rezultiralo akinetičkim mutizmom i smrću. Ataksija bez kognitivnog oštećenja, ukočenosti ili poremećaja pokreta neuobičajena je klinička slika bolesti koja ima stopu incidencije 1:1 000 000. Suvremene dijagnostičke metode u smislu naprednijih mogućnosti MR mozga i RT-QuIC uklanjaju potrebu za kompliciranom i potencijalno infektivnom biopsijom mozga u dijagnosticiranju sCJD-a. Uz prikaz slučaja donosimo kratak, ali sveobuhvatan pregled literature o suvremenim podacima o sCJD-u. Ovaj prikaz slučaja i pregled literature služe za edukaciju kliničara o ovoj rijetkoj, ali razornoj bolesti.

Ključne riječi: ataksija, Creutzfeld – Jakobova bolest, rijetke bolesti

Introduction

Creutfeldt-Jakob disease (CJD) or spongiform encephalopathy is a rare, fast-progressing neurodegenerative disease caused by an accumulation of an abnormally folded proteinaceous substance called a prion. It is a dangerously transmissible, and uniformly fatal disease. (1,2). "Prions" named by Professor Stanley B. Prusiner are an abnormal isoform (PrPsc – sc meaning "scrapie") of a normal cellular membrane protein of undetermined function (PrPc). Their unnatural state is caused by conformational changes in their structure in which the degree of helical proportion diminishes while its β pleated sheet increases. This triggers a "domino effect" in which normal human prion proteins PrPc change their shape when in contact with the abnormal prion protein, making CJD a conformational disease. These abnormal proteins are protease resistant (in various percentages) causing accumulation and with it neuronal death, gliosis, and vacuolation with atrophy hence the name "spongiform" (1). Depending upon the destruction of a particular part of the brain (be it frontal, parietal, occipital, temporal cortex or basal ganglia, thalamus, or cerebellum), genetic variant in 129 codon on 20. chromosome, and molecular prion type (MM1, MM2, VV1, VV2, MV1, MV2) or the cause of initial prion accumulation there are various clinical presentations. All of that makes the correct diagnosis even more difficult. Different causes of initial prion coming of existence is what differentiate CJD into sporadic (85% of cases, etiology unknown), hereditary (10-15%), acquired disease (less than 1%) (kuru, iatrogenic, and variant). Even though sCJD is the most represented form of CJD its rarity is attested by the fact that its annual incidence is 1 to 2 cases per million of the population worldwide, and in the case of sCJD there has been a small predominance in women (1,4:1 compared to men) (2). However, its rarity does not excuse an astute clinician from not recognizing this devastating disease as its quick destructive potential on a patient and his/hers family with all treatments failing cause a leaving mark on all of those included. SCJD is most often diagnosed in elderly patients with an age of onset being between 55 and 75 years, while a median disease duration is 6 months, with patients usually expiring in the terminal stage from respiratory infection (2). Depending on presentation at the onset the symptoms of sCJD are fast cognitive decline (72% of patients at onset), ataxia (72% onset), pyramidal symptoms (40% onset), myoclonus (40% onset), extrapyramidal symptoms (36% onset), visual disturbances (38% onset), paresthesia (13% onset), akinetic mutism (9% onset), and epileptic seizure (3% onset) (2). Divergence from the typical sCJD clinical picture should not lead a clinician from a diagnostic path as atypical variations of sCJD such as the Heidenhaim variant (prominent central visual symptoms such as anopia) and Brownell-Oppenheimer variant (cerebellar ataxia as an only neurological symptom present in weeks) have been

reported and known for years (3,4). While definitive diagnosis is only made possible by biopsy or autopsy, 2018. CDC criteria recognize probable diagnosis (positive clinical features combined with positive RT-QuIC in CSF/other tissues or typical EEG with triphasic periodic sharp wave complexes, positive 14-3-3 CSF assay, brain MRI with high signal in caudate/putamen, or two cortical regions visible on DWI/FLAIR) and possible CJD diagnosis (clinical features + duration of disease less than 2 years + alternative diagnosis excluded) (5). If not diagnosed at right time it can often end fatally before a final diagnosis is met. It is important to exclude potentially treatable causes. We present an atypical case of an sCJD which struck us by surprise, as the patient initially complained only of diplopia, and balance issues, with no complaints concerning memory or movement disorders.

Case report

A 57-year-old woman, with ulcerative colitis in the past medical history, was referred to our emergency department by her general practitioner for evaluation of a 2-week history of gait unsteadiness. She complained of progressive stance and gait instability along with trunkal and limb ataxia. She also reported a visual disorder that she described as a form of oscillopsia (her vision shimmered, unable to focus), with general complaints of anorexia and unintentional weight loss. During the initial interview in the neurological emergency infirmary, the patient did not exhibit obvious cognitive dysfunction, her neurological examination revealed subtle dysarthria, diplopia with left gaze, wide-based ataxic gait with occasional small steps, sinistropulsion in Romberg position, and ataxia of the limbs, predominantly of the left arm. The brain CT performed in the emergency department did not show evidence of any significant lesions. Initially hospitalized as an ataxia of unknown cause the diagnostic workup went on to exclude more common disorders of coordination and vertigo. Upon the more detailed taking of medical history, the patient was revealed to have subtle difficulties in reconstructing details from her life. Montreal Cognitive Assessment (MoCA testing) was done and revealed a surprising 21/30 result. Afterward, detailed medical history of the patient was taken from the patient family members who stated that she has had a periodically reduced attention span in the last couple of months, they also reported impairment of short-term memory and language difficulties in the form of subtle occasional dysarthria and comprehension difficulties. They also noticed certain behavioral changes a couple of months before, she became overprotective over her grandchildren, bad-tempered, and withdrawn. Her family denied myoclonic jerks, tremors, and other involuntary movements, or psychotic features. There was no history of major surgery or blood transfusion, corneal transplantation, or traveling to the tropics and subtropical regions. Laboratory results including basic full blood count, metabolic panel, hepatitis B and C, human immunodeficiency virus, autoimmune diseases screen and tumor markers, vitamin B12 and folate acid, and thyroid hormone levels were unremarkable. Biochemical and cytological analysis of CSF was also unremarkable, bacterial culture and test for viral encephalitis (HSV, VZV, *morbilli, mumps*) from the CSF sample excluded infectious disease. On the fourth day of hospitalization brain MRI was performed and revealed slightly increased signal intensity from the head and body of n. caudatus on the left side on T2 and FLAIR sequences (images 1.-4.). Restricted diffusion in the DWI sequence was also observed in multiple cortical areas bilaterally, predominantly left frontal, parietal, and occipital cortex (images 5.-7.).

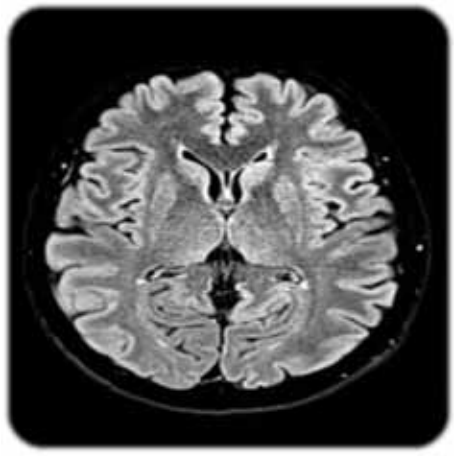


Fig. 1. FLAIR increase of signal of the head of left N. Caudatus

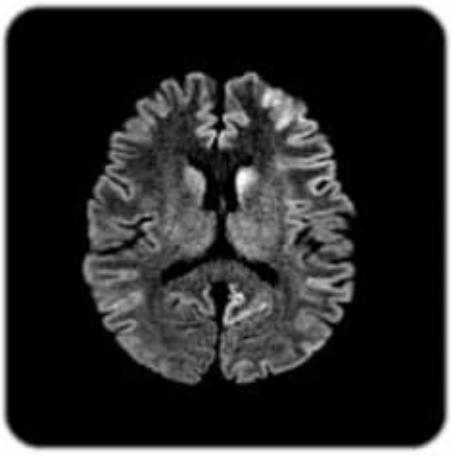


Fig. 2. DWI sequence N. Caudatus

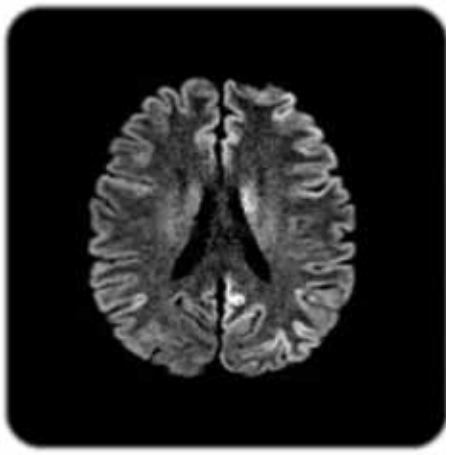


Fig. 3. DWI sequence N.Caudatus

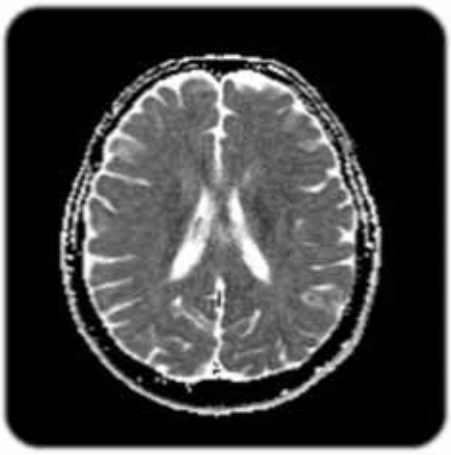


Fig. 4. ADC sequence N.Caudatus

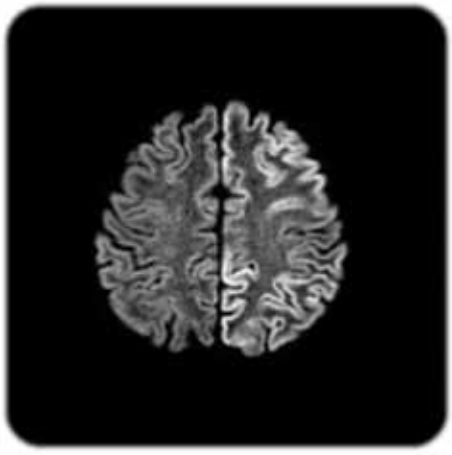


Fig. 5. DWI sequence frontal and parietal cortex with cortical ribboning.

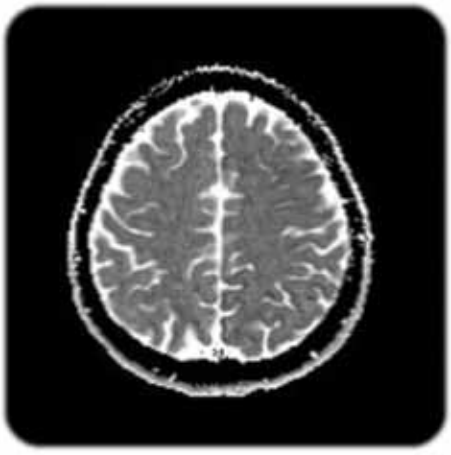


Fig. 6. ADC sequence frontal and parietal cortex signal change.

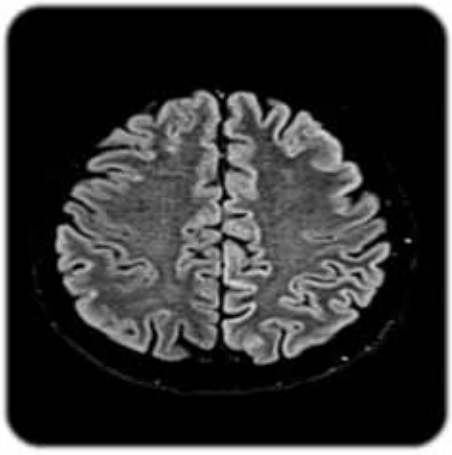


Fig. 7. FLAIR sequence frontal and parietal cortex

Thanks to an experienced neuroradiologist and a treatment team consisting of movement disorder specialists, and epilepsy specialists, a diagnosis of possible prion disease was made. Further confirming our suspicions EEG showed bilateral frontal slowing with typical intermittent triphasic waves, and delta activity, mostly left frontotemporal (image 9.-10.).

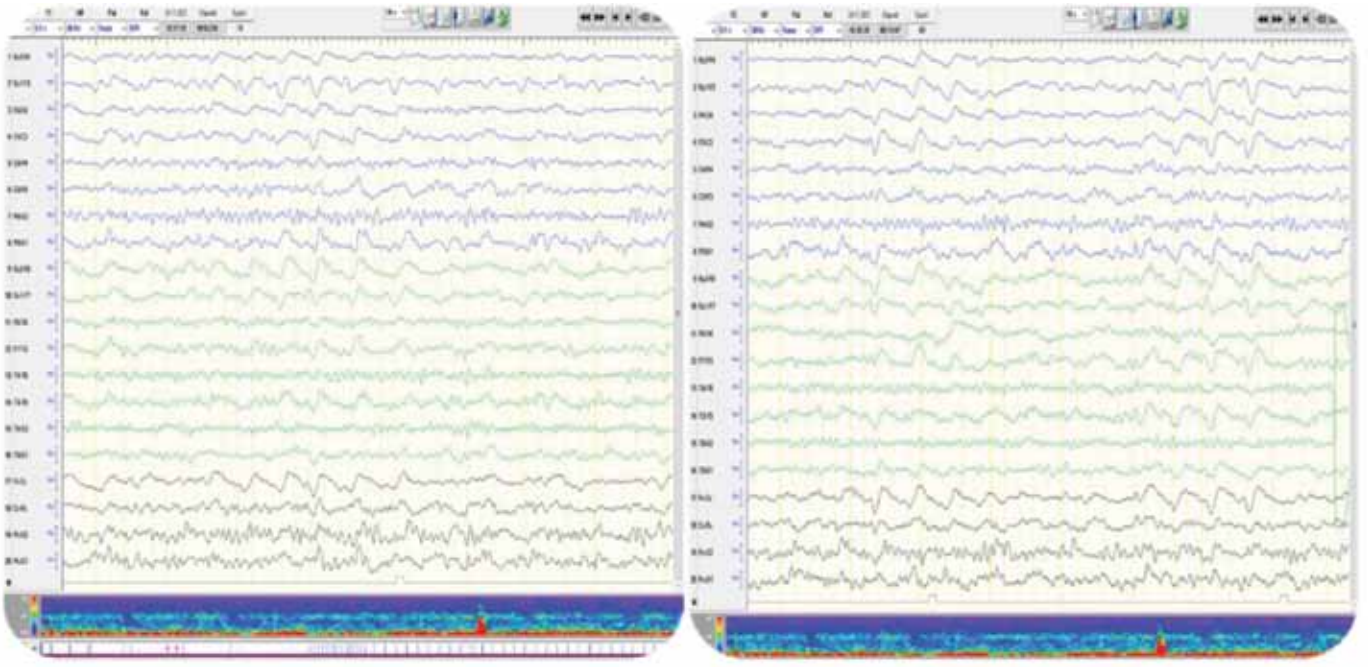


Fig. 9.-10. Typical triphasic waves are seen mostly in an area of the left frontotemporal cortex, and bifrontal cortex.

A CSF sample was sent to be confirmed with the *real-time quaking-induced conversion* (*RT-QuIC*) and it was positive. A diagnosis of probable sCJD was made with both the leading neurologist and the family members not being in favor of a confirmatory biopsy. The patient's family members were thoroughly informed about the disease process, the unfortunate lack of a cure, and further prognosis. Fulfilling the wishes of the patient and the patient's family members detailed information regarding the disease process was mercifully withheld from the patient. At the time of discharge from the hospital (13 days of hospitalization), the patient was slightly disorientated in time, but well-orientated in place and to a person with progressive moderate cognitive decline, besides those impairments, neurological examination was stationary in comparison with the first examination. 5 days after discharge from our Department, she was admitted to our Emergency Department because of exacerbation of her symptoms in the form of complete inability to walk, variable disorientation in time, space, to herself and persons around her, and a deterioration of other cognitive functions. She was complaining of blurred vision and worsening of prior visual disturbances and she was unable to follow simple verbal commands. Routine blood and urine tests were within normal limits. Chest X-Ray and brain CT were unremarkable. She was discharged from the hospital and sent to home treatment as per the wishes of the family. Arrangements were made for home care by the family members which was afterward escalated to hospice care. Four weeks later, she was readmitted to the emergency department because of a disturbance of consciousness. She presented in a state of akinetic mutism, with bilateral spontaneous horizontal nystagmus and rigor bilaterally, more marked on the left side. Blood test and chest X-Ray were normal, urine examination showed a urinary tract infection. Despite supportive and palliative treatment patient, unfortunately, expired three months after the onset of the symptoms. As per the wishes of the family autopsy of the patient was not performed.

CLÍNIC BARCELONA Hospital Universitari

Informe Parcial

Centre de Diagnòstic Biomèdic

Nombre: [redacted]
Fecha Nacimiento: [redacted]
s/Referencia:
Nº Petición CDB: [redacted]
Fecha Recepción: [redacted]
Fecha Finalización: [redacted]

ALTRES (NOMES PER LABORATORIS)

	RESULTADO	UNIDADES	VALOR REFERENCIA
INMUNOLOGIA CLINICA			
INMUNONEUROLOGIA			
Detección de proteína priónica para el diagnóstico de la Enfermedad de Creutzfeldt-Jakob, LCR	Positive		

Interpretación

SAMPLE: Cerebrospinal fluid

REASON FOR CONSULTATION: Suspected Creutzfeldt-Jacob disease.

METHODOLOGY: Real-time quaking-induced prion protein conversion (RT-QuIC).

According to McGuire LI *et al* (2012) this tecnique showed a sensitivity and specificity of 89% and ~100%, for the diagnosis of sporadic Cretzfeldt-Jakob.

RESULT: POSITIVE

INTERPRETATION / CONCLUSION: The positive test, on a compatible clinical context, is highly suggestive of Creutzfeldt-Jakob disease.

If you are interested in doing genetic studies of the prion protein gene to determine the polymorphism of codon 129 or screening for mutations, please send us 20 ml of fresh blood (no need to refrigerate) in tubes containing citrate or EDTA as an anticoagulant and 5 ml of serum as well as a copy of informed consent for genetic study.

TECHNICAL LIMITATIONS: This interpretation is subject to compliance with the preanalytical conditions set by the CDB.

Assay certified by:

Fig. 11. Positive RTQuIC which was analyzed at an partner facility.

Discussion

Being that our patient initially presented with symptoms of ataxia, diplopia, and slight dysarthria our initial suspicion was of cerebrovascular disease of posterior circulation, metabolic, toxic, or autoimmune encephalopathy. Subtle cognitive changes were masked by the high education of our patient who continued to read and solve newspaper quizzes during an initial couple of days of hospitalization. Only through detailed history taking, and analysis did we find initial neuropsychiatric symptoms which were corroborated by family members' statements, and confirmed with a low MoCA score. Standard and extended biochemical, cytological, and infectious analysis of both serum and CSF was normal, excluding meningitis, encephalitis, and toxic and metabolic encephalopathy. At this stage, a high level of suspicion is needed to guide a clinician to the right diagnosis as a brain MRI was reported positive for prion disease thanks to the experience and coordination of our neuroradiologist and neurological team. Medical history and neurological status combined with brain MRI data, and then EEG data further solidified probable sCJD diagnosis. RT-QuIC results from CSF confirmed the diagnosis as probable sCJD excluding other differential diagnoses. With only supportive treatment the patient, unfortunately, expired 3 months after the onset of symptoms.

Symptoms of sCJD are numerous and present a highly recognizable syndrome if the clinician is wary of possible prion disease in a population. But these symptoms are hardly specific for CJD. Different types of CJD present different clinical pictures. Recent use of genetic sequencing and high-end diagnostic workout has enabled detailed identification of different types of sCJD depending on polymorphism of the prion gene PRNP at the codon 129 (either methionine M or valine V) and prion molecule type (type 1 or 2). These subtypes differ in the initial neuroanatomical location of prion accumulation and with its initial symptoms, while ancillary testing using MRI, EEG, and CSF tests are mostly positive in similar percantages. Frequent types are: MM1/MV1 (median age 68, median disease duration 4 months) is the most common form with diffuse cortical and thalamic involvement causing early dementia, ataxia, myoclonus, and visual disturbance, MV2 (median age 65, median disease duration 17 months) with slowly progressive ataxia, dementia, and extrapyramidal symptoms, VV2 (median age 64, median disease duration 6.5 months) severe ataxia, late dementia, early severe cerebellum involvement. Rare types are: MM2 affecting thalamus (median age 52, median disease duration 16 months) causes insomnia and agitation early on, followed by ataxia and cognitive changes, MM2 cortical (median age 64, median disease duration 16) causing progressive dementia which lasts for months, VV1 (median age 44, median disease duration 21) younger patients affected with slowly progressive dementia, ataxia, and extrapyramidal symptoms, MM1 with amyloid plaques (median age 58, median disease duration 22) slower variant of typical MM1 only discernable by typical amyloid PrP plaques on biopsy or autopsy. Hereditary CJD is distinguished by positive family history thanks to autosomal dominant mutations in the PRNP gene, younger age of presentation, with Gerstmann-Straussler-Scheinkerand syndrome, and Fatal Familial Insomnia biomarkers and MRI is inconclusive. Iatrogenic CJD requires a history of transplantation or medical device implantation, while variant CJD needs a direct animal-to-human transmission (typical MRI pulvinar signal intensity, EEG, CSF, and RtQuIC inconclusive) (6). Being that sCJD is a diagnosis with no active treatment and therefore terminal it is first necessary to exclude potentially treatable causes of ataxia and/or fast-progressing dementia. Usually, the most similar clinical presentation to sCJD with its subacute cognitive impairment, psychiatric symptoms, ataxia, movement disorders, and seizures is attributed to autoimmune and paraneoplastic encephalitis. Brain MRI changes are similar with some characteristic differences such as typical predisposition for limbic localization of

FLAIR/T2W hyperintensity, subcortical hyperintensity, and cerebellar involvement usually not seen in sCJD. Positive autoantibodies and cancer biochemical markers with radiological confirmation of a neoplasm alongside a positive medical history of weight loss and previous nonspecific symptoms (fever, fatigue) steer the clinical diagnosis in this direction. Infective meningoencephalitis besides its symptoms of encephalopathy is often followed by high fever, headache, and neck stiffness. What differentiates this illness from sCJD is its positive epidemiology, serum and CSF immune markers (elevated protein, leukocyte count, change in glucose), positive bacterial culture, positive PCR (for HSV, EBV, JC, West Nile virus, etc.), more pronounced memory loss, and a tendency for seizure with mesial temporal signal changes in MRI in case of viral encephalitis. JC granule cell neuronopathy should be suspected when confronted with progressive ataxia, and dysarthria in immunocompromised patients. Positive PCR for the JC virus, impressive cerebellar atrophy, and cerebellar signal changes make a distinction against sCJD. Protracted hypoglycemia in diabetic patients or patients with hypermetabolic glucose consumption on rare occasions produces a similar clinical picture with seizures, movement disorders, consciousness disorders, and similar brain MRI findings affecting cortical areas and basal ganglia. Nonketotic hyperglycemia-induced hemichorea as a differential diagnosis presents contralateral basal ganglia T1 hyperintensity with absent T2, FLAIR, or DWI changes. Biochemical analysis and analysis of preceding events usually resolve both issues. Mimicking brain MRI changes similar to sCJD have been reported in patients coming out of status epilepticus, however, their transient nature is confirmed with a control MRI scan discerning them from sCJD. Patients with severe hepatic disorder and hyperammonemia provide a similar pallete of symptoms and MRI signal changes but are differentiated from sCJD by the severe metabolic state of the patient usually responding well to the treatment of hyperammonemia. Inadvertent swift recovery of hypoosmolar or hyperosmolar states with its hemiparesis, pseudobulbar palsy, consciousness disorders, and bilateral FLAIR/T2 hyperintensity in basal ganglia is similar to sCJD while medical history, previous electrolyte disbalance, rapid symptom onset, and lack of DWI hyperintensity makes a distinction from sCJD. Wilson disease and Wernicke encephalopathy are easily treatable subacute encephalopathies with movement disorders, ataxia, and cognitive changes different from sCJD by limited cortical involvement and more pronounced basal ganglia involvement on brain MRI with readily recognizable copper, and thiamin deficiency in biochemical analysis. They should be among the first suspects excluded as they are readily treatable, and respond favorably to acute treatment (7). When presented with progressive dementia, sCJD is often mistaken for rapid Alzheimer's disease, and while AD can present with myoclonus, positive EEG and 14-3-3 it has substantial temporal and hippocampal cortical atrophy detected on MRI (cortical atrophy is minimal in sCJD) with sCJD and ADs incident rate diverging as age progresses. Other dementias such as Lewy body dementia, and frontotemporal dementia together with atypical Parkinson's disease (such as progressive supranuclear palsy, and corticobasal degeneration) besides typical and readily recognizable symptoms are slower progressing than sCJD with life spans after diagnosis measured in years compared to months (8,9). The only diagnostic method providing a definitive diagnosis of CJD is a biopsy of the affected brain tissue or tonsils (in vCJD). Paradoxically the biopsy of CJD patients has reported low positive diagnostic rates, with low changes in treatment protocols questioning its utility. Dangers of proceeding with biopsy due to high infectiousness are nowadays reserved for resolving high suspicions of a treatable disease or only in the last ditch effort of diagnosing atypical cases of CJD. Confirmatory biopsies or autopsies are nowadays omitted in favor of noninvasive diagnostic tests with high specificity such as RTQuIC (10). Extended analysis of blood serum, and CSF are used to exclude sCJD mimics. Brain CT is usually normal, only in late stages presenting with nonspecific cortical atrophy (1). Diagnostics that have the highest yield in terms of positive diagnostic outcome are MRI (especially DWI, FLAIR/T2W sequence), EEG, and RT-QuIC from CSF. Technological solutions of brain MRI have proven themselves to be an excellent primary method in diagnosing CJD. The sensitivity of an MRI in diagnosing CJD currently exceeds even those of CSF biomarkers such as 14-3-3 proteins, neuron-specific enolase, and T-tau (11) Sensitivity of brain MRI in detecting sCJD is reported to be 91% with reported 95% specificity. Unfortunately, routine MRI is normal in as much as 21% of patients with early sCJD, with later visible changes presented with advancing stages of the disease (12,13). The most sensitive sequence to identify characteristic changes is diffusion-weighted imaging (e.g. b=1000) which demonstrates an increased signal, that is more conspicuous than either T2/FLAIR changes or ADC abnormalities. ADC is variable and depends on timing. In the early phase, low values may be seen before marked changes in DWI or visible FLAIR changes, and at a late phase pseudonormalised or facilitated and associated with atrophy. T2-FLAIR hyperintensity is more subtle than DWI changes and may be absent early in the course of the disease (7,14-16). DWI sequence is especially useful with uncooperative patients with as little as 30 seconds needed for image acquisition. Vacuolation of brain tissue restricting water molecule diffusion presents a positive image even in patients with a mild clinical presentation with negative EEG, and CSF biomarkers (12). Typical MRI presentations of CJD include cortical ribboning (hyperintense signal in the cerebral cortex), a hyperintense signal in the caput of nuclei caudate, putamen, and thalamus (double hockey sign, and pulvinar sign more specific for vCJD) (13). SCJD imaging is remarkable for the absence of signal change in the cerebellum besides atrophy even though a high burden of

cerebellar symptoms would suggest otherwise (7). Furthermore, sCJD lesions have no gadolinium uptake (14-16). EEG presents as another highly accessible diagnostic method with typical triphasic sharp wave complexes and less specific but equally important burst wave suppression patterns. Characteristic triphasic sharp wave complexes in EEG are present in 67% of patients with sCJD, problematic aspect is that they may not develop until late in the disease course (usually 12 weeks after symptom onset) and may disappear with disease progression. Repetitive EEG recording raises the sensitivity to 90% and specificity to 86% (12,17). Characteristic symptoms of fast-progressing dementia, myoclonic jerks, and positive triphasic sharp wave EEG activity can be absent in at least 25% of sCJD patients (12). A recent advancement in biomarker diagnostics in the form of real-time quacking-induced conversion (RT-QuIC) analysis of CSF has an astonishing sensitivity of 92% and specificity of 100%. It uses the ability of the misfolded prion protein from CSF to change the confrontation of normal PrP into a misfolded form which is then monitored using a fluorescent dye. The properties of this technique have made it essential in the modern diagnostics of CJD. Guidelines acknowledge patients with neuropsychiatric symptoms, and positive RT-QuIC as probable sCJD without the need for other tests to be positive (18,19). RT-QuIC as a method is imperfect in its cost, and availability. In case of inability to perform RT-QuIC other more traditional CSF biomarkers are also more than useful. Among them Total (t)-tau has proven to be the best surrogate CSF marker with 91.3% sensitivity and 78.9% specificity, after which comes 14-3-3 (ELISA 85.4% sensitivity, 68.8% specificity; Western blot 78.9% sensitivity, and 66.1% specificity), and neurofilament light chain protein NfL (>95% sensitivity, but 43.1% specificity) (20). The quest for finding the definitive cure for CJD has been long and unfortunately unfruitful. Starting with amantadine with only observational studies speculating on its antiviral properties, no effect on disease progress was made with only scarce clinical improvement (21). The first randomized double-blind controlled study of a drug in CJD was conducted with flupirtine having a transient beneficial effect on cognitive functions with no effect on survival time (21,22). Initially tried as compassionate treatment in observational studies quinacrine with its ambiguous results (unsubstantial clinical improvement with no effect on survival time) was finally put to rest in another double-blind randomized controlled study which found no effect of quinacrine on the survival of patients with sCJD (21,23). As is with quinacrine initially positive experimental outcomes and hypotheses in observational studies of doxycycline proved not applicable in a randomized controlled study (21). It is only with the intrathecal application of pentosan polysulphate that substantial improvement in survival time was found but only in patients with vCJD (21). Research is ongoing with the first experimental treatment of CJD patients with anti-PrPc monoclonal antibody (PRN100) reported (24). Alternative to animal studies human cerebral organoids are proposed as a novel model for screening future CJD drugs potentially accelerating the process (25). Many of the aforementioned drugs showed their hypothetical positive effect in the in vitro or experimental animal studies with early phases of CJD. These states are hardly translatable to the current state of human CJD cases. However, proof that RCT is possible in this rare disease, and more pronounced public consciousness of this disease together with guided international surveillance strategies provide reasons to be hopeful for the future. Correct diagnosis of CJD is important even though there are still no specific ways of treating this disease. The patient and their family/caregiver(s) must be spared the frustration of uncertainty and inadequate therapy. Knowledgeable, and compassionate clinicians, proper informing of the patient, family members/caregivers, and guidance in the process of neuropalliative care can give enough time to accept, and prepare for the inevitable end, and with correct symptomatic treatment temporally alleviate discomfort (26).

Referencess

1. Ropper AH, Samuels MA, Klein JP, Prasad S. Viral Infections of the Nervous System and Prion Diseases. In: Ropper AH, Samuels MA, Klein JP, Prasad S. (eds.). Adams and Victor's Priniciples of Neurology. 11th edition. New York: Mc Graw Hill; 2019: 763-797.
2. Zerr I, Parchi P. Sporadic Creutfeldt-Jakob disease. In: Pocchiari M, Manson J (eds.). Handbook of Clinical Neurology, Human Prion Diseases. 2018;vol. 153 (3rd series):155-174. https://doi.org/10.1016/B978-0-444-63945-5.00009-X.
3. Kropp S, Schulz-Schaeffer WJ, Finkenstaedt M, Riedemann C, Windl O, Steinhoff BJ, Zerr I, Kretzschmar HA, Poser S. The Heidenhain variant of Creutzfeldt-Jakob disease. Arch Neurol. 1999;56(1):55-61. doi: 10.1001/archneur.56.1.55.
4. Brownell B, Oppenheimer DR. An ataxic form of subacute presenile polioencephalopathy (Creutzfeldt-Jakob disease). J Neurol Neurosurg Psychiatry.1965;28(4):350-61. doi: 10.1136/jnnp.28.4.350.
5. Department of Health and Human Services, Centers for Disease Control and Preventio, Creutzfeldt-Jakob Disease, Classic (CJD), 2018. https://www.cdc.gov/prions/cjd/diagnostic-criteria.html, accessed on November 12 2022.
6. Baldwin KJ, Correl CM. Prion Disease. Semin Neurol. 2019;39(4):428-439. doi: 10.1055/s-0039-1687841.
7. Fragoso DC, Gonçalves Filho AL, Pacheco FT, Barros BR, Aguiar Littig I, Nunes RH, Maia Júnior AC, da Rocha AJ. Imaging of Creutzfeldt-Jakob Disease: Imaging Patterns and Their Differential Diagnosis. Radiographics. 2017;37(1):234-257. doi: 10.1148/rg.2017160075.
8. Kojima G, Tatsuno BK, Inaba M, Velligas S, Masaki K, Liow KK. Creutzfeldt-Jakob disease: a case report and differential diagnoses. Hawaii J Med Public Health. 2013;72(4):136-9. PMID: 23795314; PMCID: PMC3689509.
9. Van Everbroeck B, Dobbeleir I, De Waele M, De Deyn P, Martin JJ, Cras P. Differential diagnosis of 201 possible Creutzfeldt-Jakob disease patients. J Neurol. 2004;251(3):298-304. doi: 10.1007/s00415-004-0311-9.
10. Manix M, Kalakoti P, Henry M, Thakur J, Menger R, Guthikonda B, Nanda A. Creutzfeldt-Jakob disease: updated diagnostic criteria, treatment algorithm, and the utility of brain biopsy. Neurosurg Focus. 2015;39(5):E2. doi: 10.3171/2015.8.
11. Forner SA, Takada LT, Bettcher BM, Lobach IV, Tartaglia MC, Torres-Chae C, Haman A, Thai J, Vitali P, Neuhaus J, Bostrom A, Miller BL, Rosen HJ, Geschwind MD. Comparing CSF biomarkers and brain MRI in the diagnosis of sporadic Creutzfeldt-Jakob disease. Neurol Clin Pract. 2015;5(2):116-125. doi: 10.1212/CPJ.0000000000000111.
12. Mao-Draayer Y, Braff SP, Nagle KJ, Pendlebury W, Penar PL, Shapiro RE. Emerging Patterns of Diffusion-Weighted MR Imaging in Creutzfeldt-Jakob Disease: Case Report and Review of the Literature. AJNR Am J Neuroradiol. 2002; 23(4): 550–556. PMCID: PMC7975110PMID: 11950643.
13. Spero M, Lazibat I. Creutzfeldt-Jakob disease: case report and review of the literature. Acta Clin Croat. 2010;49(2):181-7. PMID: 21086738.
14. Vitali P, Maccagnano E, Caverzasi E et al. Diffusion-Weighted MRI Hyperintensity Patterns Differentiate CJD from Other Rapid Dementias. Neurology. 2011;76(20):1711-9. doi:10.1212/wnl.0b013e31821a4439.
15. Cohen OS, Hoffmann C, Lee H, Chapman J, Fulbright RK, Prohovnik I. MRI detection of the cerebellar syndrome in Creutzfeldt-Jakob disease. Cerebellum. 2009;8(3):373-81. doi: 10.1007/s12311-009-0106-8.
16. Valente A, Pinho P, Lucato L. Magnetic Ressonance Imaging in the Diagnosis of Creutzfeldt-Jakob Disease: Report of Two Cases. Dement Neuropsychol. 2015;9(4):424-7. doi:10.1590/1980-57642015DN94000424.
17. Steinhoff BJ, Räcker S, Herrendorf G, Poser S, Grosche S, Zerr I, Kretzschmar H, Weber T. Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt-Jakob disease. Arch Neurol. 1996;53(2):162-6. doi: 10.1001/archneur.1996.00550020074017.
18. Reddy VD, Hamed A, Settipalle N, Jande S, Rahman S, Szabella ME, Boghossian J. Real-time Quaking-induced Conversion Assay for the Diagnosis of Sporadic Creutzfeldt-Jakob Disease in a Living Patient. Infect Dis (Auckl). 2019;12:1178633719874797. doi: 10.1177/1178633719874797.
19. Chatzikonstantinou S, Kazis D, Karantali E, Knights M, McKenna J, Petridis F, Mavroudis I. A meta-analysis on RT-QuIC for the diagnosis of sporadic CJD. Acta Neurol Belg. 2021;121(2):341-349. doi: 10.1007/s13760-021-01596-3.
20. Abu-Rumeileh S, Baiardi S, Polischi B, Mammana A, Franceschini A, Green A, Capellari S, Parchi P. Diagnostic value of surrogate CSF biomarkers for Creutzfeldt-Jakob disease in the era of RT-QuIC. J Neurol. 2019;266(12):3136-3143. doi: 10.1007/s00415-019-09537-0.
21. Vetrugno V, Puopolo M, Cardone F, Capozzoli F, Ladogana A, Pocchiari M. The future for treating Creutzfeldt–Jakob disease. Expert Opinion on Orphan Drugs. 2015;3(1):57-74. doi: 10.1517/21678707.2015.994605.
22. Otto M, Cepek L, Ratzka P, Doehlinger S, Boekhoff I, Wiltfang J, Irle E, Pergande G, Ellers-Lenz B, Windl O, Kretzschmar HA, Poser S, Prange H. Efficacy of flupirtine on cognitive function in patients with CJD: A double-blind study. Neurology. 2004;62(5):714-8. doi: 10.1212/01.wnl.0000113764.35026.ef.
23. Geschwind MD, Kuo AL, Wong KS, Haman A, Devereux G, Raudabaugh BJ, Johnson DY, Torres-Chae CC, Finley R, Garcia P, Thai JN, Cheng HQ, Neuhaus JM, Forner SA, Duncan JL, Possin KL, Dearmond SJ, Prusiner SB, Miller

BL. Quinacrine treatment trial for sporadic Creutzfeldt-Jakob disease. Neurology. 2013;81(23):2015-23. doi: 10.1212/WNL.0b013e3182a9f3b4.
24. Mead S, Khalili-Shirazi A, Potter C, Mok T, Nihat A, Hyare H, Canning S, Schmidt C, Campbell T, Darwent L, Muirhead N, Ebsworth N, Hextall P, Wakeling M, Linehan J, Libri V, Williams B, Jaunmuktane Z, Brandner S, Rudge P, Collinge J. Prion protein monoclonal antibody (PRN100) therapy for Creutzfeldt-Jakob disease: evaluation of a first-in-human treatment programme. Lancet Neurol. 2022;21(4):342-354. doi: 10.1016/S1474-4422(22)00082-5.
25. Groveman BR, Ferreira NC, Foliaki ST, Walters RO, Winkler CW, Race B, Hughson AG, Zanusso G, Haigh CL. Human cerebral organoids as a therapeutic drug screening model for Creutzfeldt-Jakob disease. Sci Rep. 2021;11(1):5165. doi: 10.1038/s41598-021-84689-6.
26. Harrison KL, Garrett SB, Gilissen J, Terranova MJ, Bernstein Sideman A, Ritchie CS, Geschwind MD. Developing neuropalliative care for sporadic Creutzfeldt-Jakob Disease. Prion. 2022;16(1):23-39. doi: 10.1080/19336896.2022.2043077.

Recovery of Recurrent Transient Neurogenic Stuttering due to Functional Neuroplasticity

Marina Roje Bedeković[1,2,3], Lara Pilepić[1]

[1] Neurological Intensive Care Unit, Department of Neurology, Sestre Milosrdnice University Hospital Center
[2] School of Medicine, University of Zagreb
[3] Faculty of Education and Rehabilitation Sciences, University of Zagreb

Abstract:

Although epilepsy symptoms are well established, there are only several described cases of post seizure speech fluency impairments. Epileptic activity may interfere with speech but speech impairments have the ability to recover because of neural plasticity that has been widely investigated in epilepsy population. In the available literature there is only one case report of transient neurogenic stuttering described. In this case report we describe a recovery of a 33-year-old male patient with recurrent transient neurogenic stuttering after focal idiopathic seizures due to functional neuroplasticity.

Keywords: adult-onset epilepsy, recurrent transient neurogenic stuttering, functional neuroplasticity

Sažetak

Oporavak ponavljajućeg prolaznog neurogenog mucanja zbog funkcionalne neuroplastičnosti

Iako su simptomi epilepsije poznati, postoji samo nekoliko opisanih slučajeva poremećaja tečnosti govora nakon epileptičkog napada. Epileptička aktivnost može ometati govor, ali govorna oštećenja imaju sposobnost oporavka zbog plastičnosti mozga koja je detaljno istražena u bolesnika s epilepsijom U dostupnoj literaturi opisan je samo jedan slučaj prolaznog neurogenog mucanja. U ovom prikazu slučaja opisujemo oporavak 33-godišnjeg bolesnika s ponavljajućim prolaznim neurogenim mucanjem nakon fokalnih epileptičnih napadaja zbog funkcionalne neuroplastičnosti.

Ključne riječi: epilepsija u odrasloj dobi, prolazno neurogeno mucanje, funkcionalna neuroplastičnost

OPEN ACCESS

Correspondence:
Marina Roje Bedeković
m.roje.bedekovic@gmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 15 May 2023
Accepted: 01 June 2023
Published: 26 June 2023

Citation:
Roje Bedeković M, Pilepić L. Recovery of Recurrent Transient Neurogenic Stuttering due to Functional Neuroplasticity
556=62-63 (2023): 82-84
DOI: 10.21857/yvjrdcvjjy

Introduction

Epilepsy is one of three most common neurological disease that can occur in all age groups. According to a recent study, 38% of epilepsies starts between the age of 21 and 40, with 10% of them being idiopathic (1). Even though temporal lobe seizures occur in 75% of patients (2) and can cause a complete loss of speech, most evidence on speech fluency impairments after seizures are described in case reports (3). The term neurogenic stuttering is a subtype of acquired stuttering in which disfluencies are caused by acquired brain damage in a person who did not stutter before brain damage (3). Unlike developmental stuttering, which typically begins in childhood, neurogenic stuttering can appear at any age following a neurological event or injury. Neurogenic stuttering can take many forms and can vary in severity depending on the underlying cause and the extent of the brain damage. It may involve repetitions, prolongations, or blocks of sounds, syllables, or words. In some cases, patients with neurogenic stuttering may also experience other speech difficulties, such as slurred speech or difficulty pronouncing certain sounds or words. Patients with transient neurogenic stuttering can recover their speech fluency using speech language therapy because of early brain plasticity (4). Because most epileptic seizures occur in hippocampus where brain plasticity has been proven, patients can recover from postictal speech and language disorders with early rehabilitation.

In this case report we describe a case of transient neurogenic stuttering because of a focal seizure in a young male patient that recovered with early speech therapy.

Case report

A 33-year-old male patient was hospitalized in a general hospital because of speech dysarthria and left arm weakness. Urgent brain computed tomography (CT) and computed tomography angiography (CTA) were normal. During the hospitalization an echocardiogram (ECG), transcranial doppler (TCD) and an electroencephalogram (EEG) were performed and showed no abnormalities. Magnetic resonance imaging (MRI) showed one small chronic vascular lesion in left frontal gyrus and one small oval hypodensity in frontal lobe centrum semiovale described as microhemorrhage. MRA showed no arteriovenous malformation or aneurisms. For the previous month before hospitalization, the patient had been working in a stressful environment and was sleep deprived. He was treated with acetylsalicylic acid. After discharge from the general hospital, only mild speech dysarthria persisted in his neurological status. He was referred to a speech language pathologist in Department of neurology – Sestre Milosrdnice University Hospital Center. Speech language pathologist did a thorough assessment for aphasia, dysarthria, speech apraxia and fluency disorders. Comprehensive language battery and audio-perceptual assessment showed no impairments. Fluency assessment included analysis of a representative speech sample, determination of disfluencies index, examination of secondary behaviors and assessment of speech rate. Neurogenic stuttering was diagnosed because of severe fluency impairments. After three therapies consisting of breathing techniques and speaking on a relaxed exhale, speech fluency improved to normal, and the patient didn't need any more rehabilitation. After two months he developed thrombophlebitis on his left arm and again was hospitalized in Sestre Milosrdnice University Hospital Center. As a part of a neurological examination an EEG was done that showed an epileptiform brain activity in temporal lobe and therefore oxcarbazepine treatment was introduced. During this time, no speech impairments were noticed. After five months patient was admitted to emergency department of Sestre Milosrdnice University Hospital Center because he woke up with left arm weakness and severe speech fluency difficulties. He didn't lose consciousness. CT and CTA were normal again. Speech language pathologist stated that speech fluency had the same type of impairment as seven months ago and left arm weakness was understood as Todd's paresis. He was treated with an intravenous dose of diazepam. Todd's paresis fully recovered in two hours, but speech fluency impairment remained. An MRI scan and control CT scan were performed after three and five days and showed no lesions. Patient was treated with intensive speech therapy for fluency impairments during hospitalization and was discharged with mild speech fluency disturbances and final diagnosis of idiopathic epilepsy. In a 2 week follow up no further speech fluency impairments were noted.

Discussion

In this case report we describe a young male patient with epilepsy that developed transient neurogenic stuttering. Several case reports described neurogenic stuttering after seizures but none of them described a transient form of neurogenic stuttering after seizures.

Epileptic activity can affect speech in a variety of ways, depending on the location of the seizure in the brain and the severity of the seizure (5). Some patients with epilepsy may experience speech difficulties such as slurred or slowed speech, difficulty finding words or expressing themselves, or changes in voice pitch or tone. In some described cases, focal seizures can cause brief interruptions in speech or periods of stuttering (6). Seizures can also cause sudden and unexpected changes in speech, such as speaking in a foreign accent or using inappropriate or nonsensical language (5). However, the connection between seizures and stuttering has mostly been investigated in children and some authors even suggest stuttering as a ''relative of epilepsy" (6). Neurogenic stuttering occurs as a sudden onset adult subtype of stuttering with numerous neurological causes on record (7). This form of stuttering is significantly less common than the developmental type, and as a result, it has received much less attention in research (5). What is interesting, however, is that neurogenic

stuttering as a fluency disorder is heavily seen as a symptom rather than a diagnosis. One reason to explain this one-sided perspective in the literature is that the neurophysiology of stuttering is still unclear, as it is considered a complex process (5).
Recovery of seizure symptoms is achievable because of brain plasticity (8) that has been widely investigated in epilepsy population. Brain plasticity in epilepsy population has been widely researched mostly because of a remarkable deficit recovery that hasn't been noted in other neurological diseases (9). The recovery is possibly due to a plastic reorganization in the central nervous circuitry as a results of neural damage (5). Hippocampus is one of the most common epilepsy center (9, 10). Abnormal electric activity in that brain area causes neuron damage but doesn't cause permanent neurological deficit because of high brain plasticity. The dentate gyrus which is a part of hippocampus is made of granulate cells that have been investigated for their ability to recover and change after seizure (11, 12). Our patient developed recurrent transient neurogenic stuttering after two focal seizures as a consequence of idiopathic epilepsy. He luckily recovered speech fluency during a period of 2 weeks with early speech language therapy.
With this case report we emphasize the importance of early identification of fluency disorders in patients with epilepsy in order to differentiate them from other possible acquired speech and language impairments that occur with seizures. We also emphasize the importance of early speech language therapy stimulating early neural plasticity and shortening recovery period.

Acknowledgments

We declare no conflicts of interest. The patient's consent was obtained. We did not receive any material support.

References

1. Kaur S, Garg R, Aggarwal S, Chawla SP, Pal R. Adult onset seizures: Clinical, etiological, and radiological profile. Journal of family medicine and primary care. 2018 Jan;7(1):191.
2. Gabr M, Lüders H, Dinner D, Morris H, Wyllie E. Speech manifestations in lateralization of temporal lobe seizures. Annals of neurology. 1989 Jan;25(1):82-7.
3. Van Borsel J. Acquired stuttering: A note on terminology. Journal of Neurolinguistics. 2014 Jan 1;27(1):41-9.
4. Scharfman HE. Epilepsy as an example of neural plasticity. The Neuroscientist. 2002 Apr;8(2):154-73.
5. Janszky J, Jokeit H, Heinemann D, Schulz R, Woermann FG, Ebner A. Epileptic activity influences the speech organization in medial temporal lobe epilepsy. Brain. 2003 Sep 1;126(9):2043-51.
6. Hirtz D, Thurman DJ, Gwinn-Hardy K, Mohamed M, Chaudhuri AR, Zalutsky R. How common are the "common" neurologic disorders?. Neurology. 2007 Jan 30;68(5):326-37.
7. Scharfman HE. Epilepsy as an example of neural plasticity. The Neuroscientist. 2002 Apr;8(2):154-73.
8. Walker MC, Ruiz A, Kullmann DM. Monosynaptic GABAergic signaling from dentate to CA3 with a pharmacological and physiological profile typical of mossy fiber synapses. Neuron. 2001 Mar 1;29(3):703-15.
9. Johnson EL. Seizures and epilepsy. Medical Clinics. 2019 Mar 1;103(2):309-24.
10. Lebrun Y. Stuttering and epilepsy. Journal of neurolinguistics. 1991 Jan 1;6(4):433-44.
11. Milligan TA. Epilepsy: a clinical overview. The American Journal of Medicine. 2021 Jul 1;134(7):840-7.
12. Byrne A, Byrne MK, Zibin TO. Transient neurogenic stuttering. International Journal of Eating Disorders. 1993 Dec;14(4):511-4.

Seizure freedom with vagus nerve stimulation in neurofibromatosis type 1: A case report

Asja Hodzic[*1], Andreja Bujan Kovac[2], Andrej Desnica[3], Biljana Dapic Ivancic[2], David Ozretic[4], Goran Mrak[3], Niko Njiric[3], Jakob Nemir[3], Sibila Nankovic[2], Vlatko Sulentic[2], Zeljka Petelin Gadze[2]

[1] Department of Internal Medicine, Tesanj General Hospital, Tesanj, Bosnia and Herzegovina
[2] Department of Neurology, University Hospital Centre Zagreb and School of Medicine, University of Zagreb, Referral Centre of the Ministry of Health of the Republic of Croatia for Epilepsy, Affiliated Partner of the ERN EpiCARE, Zagreb, Croatia
[3] Department of Neurosurgery, University Hospital Centre Zagreb and School of Medicine, University of Zagreb, Affiliated Partner of EUROCAN, Zagreb, Croatia
[4] Clinical Department for Diagnostic and Interventional Neuroradiology, University Hospital Centre Zagreb and School of Medicine, University of Zagreb, Zagreb, Croatia

OPEN ACCESS

Correspondence:
Asja Hodzic
hodzic.as@gmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 28 April 2023
Accepted: 01 June 2023
Published: 26 June 2023

Citation: Hodzic A, Bujan Kovac A, Desnica A, Dapic Ivancic B, Ozretic D, Mrak G, Njiric N, Nemir J, Nankovic S, Sulentic V, Petelin Gadze Z. Seizure freedom with vagus nerve stimulation in neurofibromatosis type 1: A case report 556=62-63 (2023): 86-90
DOI: 10.21857/y54jofvwem

Abstract:

Epileptic seizures in neurofibromatosis type 1 (NF1) have been a subject of investigation of numerous studies, however, their etiology has not yet been elucidated. They are usually well controlled with antiseizure medications (ASMs), but in some pharmacoresistant patients, vagus nerve stimulation (VNS) might present a complementary treatment modality. We present a 24-year-old male patient with NF1 who had temporal lobe seizures - focal autonomic seizures with impaired awareness and oroalimentary automatisms, as well as focal motor seizures with retained awareness, in addition to moderate intellectual disability. The most significant magnetic resonance (MRI) abnormalities included infiltrative changes of medulla oblongata, pons and cerebellum, as well as signal intensity changes with mild compression in the apex of the temporal lobes, insular cortex, putamen and medial part of the frontal lobe, all more prominent on the right, along with right mesial temporal sclerosis. Interictal electroencephalogram (EEG) showed two independent epileptic foci – one in the right frontocentrotemporal region and the other in the left centrotemporal region. Throughout the years, he had been treated with several ASMs in monotherapy or polytherapy without success in seizure control. *After an extensive preoperative evaluation, VNS implantation was performed and the patient has been seizure free for almost two years.* Although a palliative intervention, VNS could be a powerful tool in the treatment of these patients and even lead to seizure freedom. To the best of our knowledge, this is the first case report where seizure freedom was achieved in a patient with NF1 following VNS implantation.

Keywords: Neurofibromatosis, Pharmacoresistant epilepsy, Vagus nerve stimulation, Seizure freedom

Sažetak:

Izostanak napadaja uz stimulaciju vagusnog živca u neurofibromatozi tip 1: Prikaz slučaja

Epileptički napadaji u neurofibromatozi tip 1 (NF1) bili su predmet istraživanja brojnih studija, međutim njihova etiologija još nije razjašnjena. Obično se dobro kontroliraju antiepileptičkim lijekovima (ASM), ali kod nekih farmakorezistentnih pacijenata, stimulacija vagusnog živca (VNS) može predstavljati komplementarni modalitet liječenja. Prikazujemo 24-godišnjeg pacijenta sa NF1

koji je imao epileptične napadaje temporalnog režnja - žarišne autonomne napadaje sa poremećajem svjesnosti i oroalimentarnim automatizmima, kao i žarišne motoričke napadaje sa očuvanom svjesnosti, uz umjerene intelektualne teškoće. Najznačajnije abnormalnosti nalaza magnetne rezonancije (MRI) uključivale su infiltrativne promjene u meduli oblongati, ponsu i cerebelumu, kao i promijenjeni intenzitet signala sa blagim kompresivnim učinkom u vršcima temporalnih režnjeva, inzularnom korteksu, putamenu i medijalnom dijelu frontalnog režnja, sve izraženije s desne strane, zajedno sa znakovima mezijalne temporalne skleroze s desne strane. Interiktalni elektroencefalogram (EEG) pokazao je dva nezavisna epileptična fokusa – jedan desno frontocentrotemporalno, a drugi lijevo centrotemporalno. Tokom godina, liječen je s nekoliko ASM u monoterapiji ili politerapiji bez uspjeha u kontroli napadaja. Nakon opsežne predoperativne obrade, urađena je implantacija VNS-a i pacijent je već skoro dvije godine bez napadaja. Iako predstavlja palijativnu intervenciju, VNS bi mogao biti moćno sredstvo u liječenju ovih pacijenata, te čak dovesti i do potpune kontrole napadaja. Koliko nam je poznato, ovo je prvi slučaj u kojem je opisan izostanak napadaja kod pacijenta sa NF1 nakon implantacije VNS-a.

Ključne riječi: Neurofibromatoza, farmakorezistentna epilepsija, stimulacija vagusnog živca, izostanak napadaja

Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder first described in 1882 by Frederick von Recklinghausen. Cardinal features of this disease include multiple café-au-lait macules, Lisch nodules (iris hamartomas), intertriginous freckling and neurofibromas. It is caused by a mutation of the neurofibromin 1 gene located on chromosome 17q11.2 which encodes neurofibromin, a tumor suppressor protein. Neurofibromatosis type 1 belongs to a broad group of neurocutaneous disorders together with neurofibromatosis type 2, tuberous sclerosis, Von Hippel-Lindau disease, Sturge-Weber syndrome and many others. It is the most common of them all with a prevalence of about 1/3000 (1). In addition to its typical features, a range of neurological manifestations may be present as well, such as brain tumors, cerebrovascular disease, learning disability, behavioural problems, attention deficit, headache and epilepsy. Unidentified bright objects present a distinctive radiological finding in the form of T2-hyperintensities on magnetic resonance imaging (MRI) of the brain, usually seen in the brainstem, cerebellum, thalamus and basal ganglia (2). Although previous studies estimated that epileptic seizures occurred in approximately 4-7% of the cases, recent data suggest that the prevalence of seizures goes up to 14% (3). They are usually well controlled with antiseizure medications (ASMs), however, in some drug resistant patients, vagus nerve stimulation (VNS) might present a complementary treatment modality.

Case presentation

We present a 24-year-old male patient who was clinically diagnosed with NF1 at the age of two and had been having epileptic seizures ever since. Initially, the patient only had temporal lobe seizures - focal autonomic seizures (epigastric aura) with impaired awareness and oroalimentary automatisms, lasting for a few minutes. One year prior to presenting to our institution, he developed focal motor seizures with retained awareness as well, usually affecting his left arm. Both types of seizures occurred three to four times a month, respectively and were followed by fatigue, nausea and postictal confusion. The patient was under medical care for his comorbidities: moderate intellectual disability, arterial hypertension and osteopenia. Family history was negative for epilepsy and neurofibromatosis. Physical and neurological examinations revealed decreased limb muscle strength, multiple café au lait spots and cutaneous neurofibromas. Throughout the years, he had been treated with several ASMs in monotherapy or polytherapy: carbamazepine (CBZ), methylphenobarbital (MPB), valproate (VPA), oxcarbazepine (OXC), levetiracetam (LEV), topiramate (TPM), lacosamide (LCM), without success in seizure control. We performed a comprehensive preoperative diagnostic evaluation. The most significant magnetic resonance (MRI) abnormalities included infiltrative changes of medulla oblongata, pons and cerebellum (Figure 1), as well as signal intensity changes with mild compression in the apex of the temporal lobes, insular cortex, putamen and medial part of the frontal lobe, all more prominent on the right, along with right mesial temporal sclerosis (Figure 2). The patient also underwent continuous video-EEG monitoring, however, due to his behavior disturbances the procedure could not last longer and his mother decided to end the procedure after less than 24 hours. During that time, no seizures were observed. Interictal electroencephalogram (EEG) showed two independent epileptic foci – one in the right frontocentrotemporal region and the other in the left centrotemporal region (Figure 3). Since the patient had been diagnosed with a pharmacoresistant form of multifocal epilepsy, the multidisciplinary team decided to per-

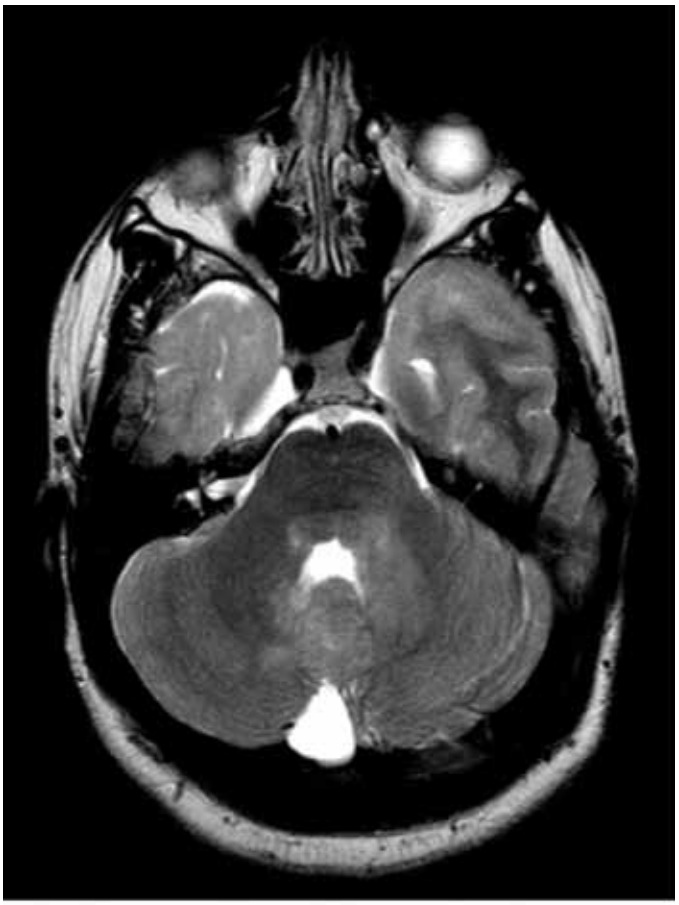


Figure 1. T2-weighted brain MRI: Axial view showing characteristic NF changes of cerebellum and brainstem.

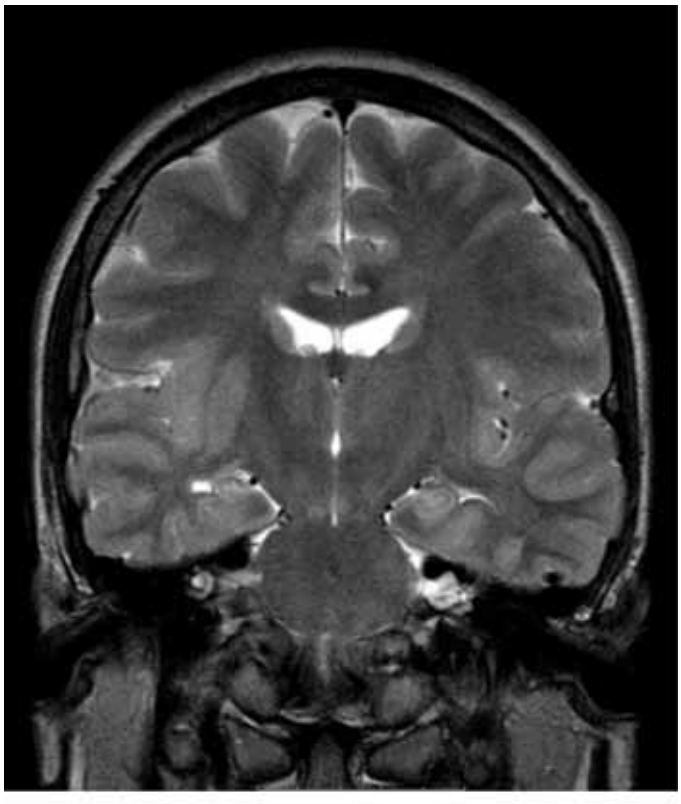


Figure 2. T2-weighted brain MRI: Coronal view showing right mesial temporal sclerosis.

form VNS implantation (LivaNova model 106), after a thorough cardiological assessment, in agreement with his parents. The postoperative course was uneventful and the patient recovered as anticipated. VNS was initiated on the fourth postoperative day at 0.25 mA and gradually increased in the following months. The patient continued taking ASMs: VPA (1500 mg), OXC (1200 mg), LCM (400 mg). Final stimulation parameters were: Output Current 2 mA, Signal Frequency 30 Hz, Pulse Width 500 μs, 30 s Signal On Time, 5 min Signal Off Time, Duty Cycle 10%; Magnet Output Current 2.25 mA, Pulse Width 500 μs, 60 s Signal On Time; AutoStim Output Current 2 mA, Pulse Width 500 μs, 60 s Signal On Time, Seizure detection ON, Heartbeat Detection (Sensitivity) 2, 30% Threshold for AutoStim. In the following months, he did not report any side effects of the VNS. He became seizure free two years after the VNS implantation and a slight dose reduction of ASMs was made: VPA (1250 mg), OXC (900 mg), LCM (400 mg). The patient has been seizure free for almost two years.

Discussion

Epileptic seizures in NF1 have been a subject of investigation of numerous studies, however, their etiology has not yet been elucidated. Approximately half of the cases of seizures in NF1 patients are structural, most frequently brain tumors, cortical and vascular malformations, whereas the role of unidentified bright objects in seizure pathogenesis has been precluded. The majority of seizures are focal in origin, which sometimes progress to bilateral tonic-clonic seizures. It is estimated that the prevalence of refractory epilepsy in patients with NF1 is 26%, compared to 30% in the general epileptic population (4). While there are several studies published in literature about the efficacy of VNS therapy in the treatment of refractory epilepsy in other neurocutaneous disorders, such as tuberous sclerosis (5, 6), scientific data about its use in NF1 are scarce. This is largely due to the fact that epilepsy, as well as drug resistant epilepsy, is less frequent in comparison to other most common neurocutaneous disorders: tuberous sclerosis and Sturge Weber syndrome (7). Moreover,

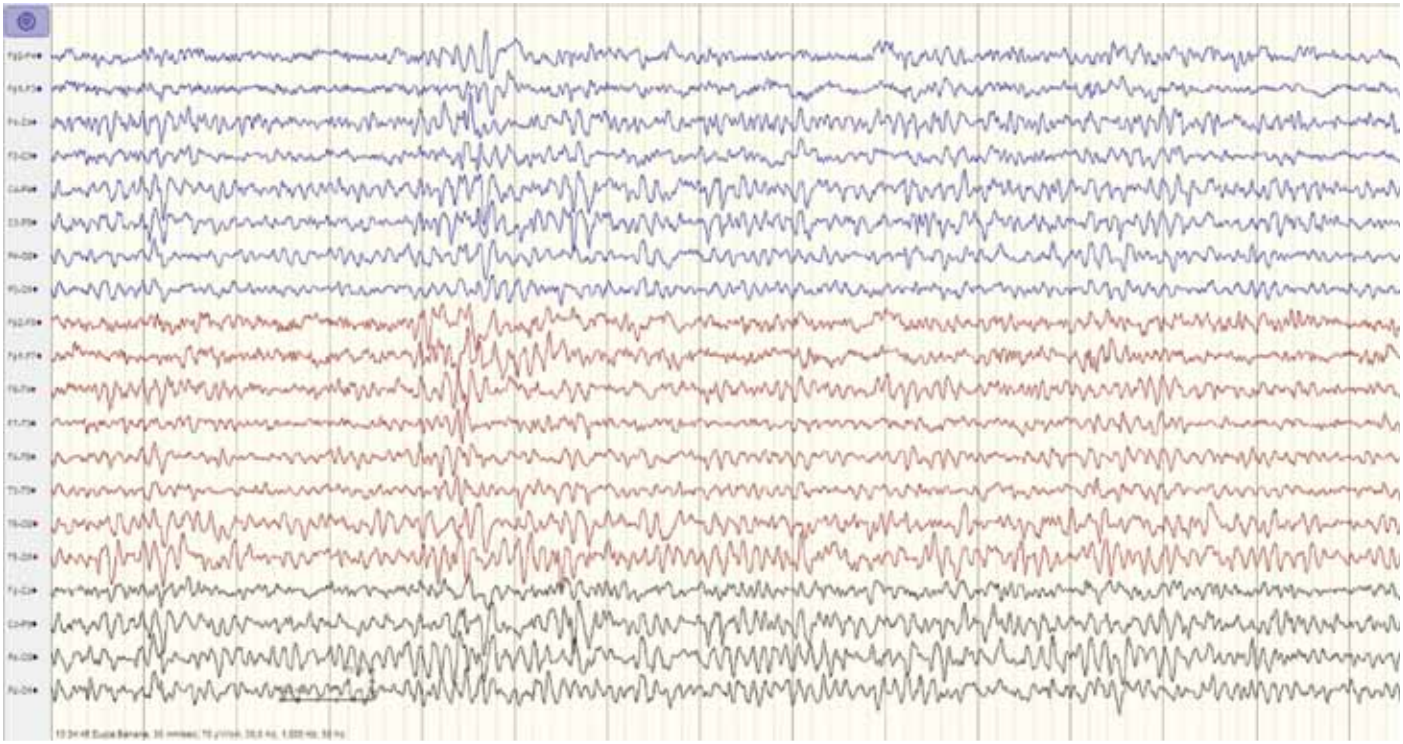


Figure 3. Interictal EEG showing slow sharp waves and spike – wave complexes right fronto – centro – temporal, mostly temporal, and slow sharp waves left centro – temporal with paroxysmal tendency of sharp waves.

an underlying pathology of the vagus nerve itself can be present as a consequence of the sole nature of the disease, for instance vagal neurofibromas, which presents a contraindication for VNS treatment. In our case, the patient had been treated with seven antiepileptic drugs with no adequate seizure control ever being achieved. Despite the fact that his MRI findings were stationary over the years, a change of semiology occurred and he developed an additional seizure type, which supports previous reports of poor electro-clinical and neuroradiological correlation between epilepsy and NF1 (8, 9). Since there was more than one epileptogenic focus, resective surgical approach was not a treatment option and VNS was the therapeutic modality that allowed the best possible seizure control for our patient. Although efficacy of adjunctive VNS therapy in refractory epilepsy has been well documented, only 8.0% of patients achieve seizure freedom (10), which is the case with our patient. Furthermore, it has been shown that VNS has a positive effect on depressive symptoms in patients with epilepsy (11) and that could provide a secondary benefit of its utility in neurofibromatosis, considering that depression is a frequent comorbidity in these patients (12).

Conclusion

Pharmacoresistant epilepsy in NF1 is a complex entity which requires a multidisciplinary approach. Our case demonstrated that VNS, although a palliative intervention, could be a powerful tool in the treatment of these patients and even lead to seizure freedom. To the best of our knowledge, this is the first case report where seizure freedom was achieved in a patient with NF1 following VNS implantation. We also want to emphasize the importance of documenting such cases and the need for carefully designed and well-conducted clinical studies to provide evidence of efficacy of VNS in this population.

Acknowledgments

The authors acknowledge no conflicts of interest. The patient's consent was obtained. We did not receive any material support.

References

1. Friedman JM. Epidemiology of neurofibromatosis type 1. Am J Med Genet. 1999 Mar 26;89(1):1-6.
2. Hsieh HY, Fung HC, Wang CJ, Chin SC, Wu T. Epileptic seizures in neurofibromatosis type 1 are related to intracranial tumors but not to neurofibromatosis bright objects. Seizure. 2011 Oct;20(8):606-11.
3. Sorrentino U, Bellonzi S, Mozzato C, Brasson V, Toldo I, Parrozzani R, Clementi M, Cassina M, Trevisson E. Epilepsy in NF1: Epidemiologic, Genetic, and Clinical Features. A Monocentric Retrospective Study in a Cohort of 784 Patients. Cancers (Basel). 2021 Dec 17;13(24):6336.
4. Bernardo P, Cinalli G, Santoro C. Epilepsy in NF1: a systematic review of the literature. Childs Nerv Syst. 2020 Oct;36(10):2333-2350.
5. Hajtovic S, LoPresti MA, Zhang L, Katlowitz KA, Kizek DJ, Lam S. The role of vagus nerve stimulation in genetic etiologies of drug-resistant epilepsy: a meta-analysis. J Neurosurg Pediatr. 2022 Mar 18:1-14.
6. Tong X, Wang X, Qin L, Zhou J, Guan Y, Teng P, Wang J, Yang Y, Li T, Luan G. Vagus nerve stimulation for drug-resistant epilepsy induced by tuberous sclerosis complex. Epilepsy Behav. 2022 Jan;126:108431.
7. Stafstrom CE, Staedtke V, Comi AM. Epilepsy Mechanisms in Neurocutaneous Disorders: Tuberous Sclerosis Complex, Neurofibromatosis Type 1, and Sturge-Weber Syndrome. Front Neurol. 2017 Mar 17;8:87.
8. Serdaroglu E, Konuskan B, Karli Oguz K, Gurler G, Yalnizoglu D, Anlar B. Epilepsy in neurofibromatosis type 1: Diffuse cerebral dysfunction? Epilepsy Behav. 2019 Sep;98(Pt A):6-9
9. Shin A, Byun JC, Hwang SK, Kwon S, Lee YJ. Clinical Characteristics of Epilepsy and Its Risk Factors in Neurofibromatosis Type 1: A Single-Center Study. Ann Child Neurol. 2021;29(1):1-7.
10. Englot DJ, Rolston JD, Wright CW, Hassnain KH, Chang EF. Rates and Predictors of Seizure Freedom With Vagus Nerve Stimulation for Intractable Epilepsy. Neurosurgery. 2016 Sep;79(3):345-53.
11. Assenza G, Tombini M, Lanzone J, Ricci L, Di Lazzaro V, Casciato S et al. Antidepressant effect of vagal nerve stimulation in epilepsy patients: a systematic review. Neurol Sci. 2020 Nov;41(11):3075-3084.
12. Houpt AC, Schwartz SE, Coover RA. Assessing Psychiatric Comorbidity and Pharmacologic Treatment Patterns Among Patients With Neurofibromatosis Type 1. Cureus. 2021 Dec 7;13(12):e20244.

A rare case of multiple unruptured intracerebral aneurysms

Matea Prenc[*1], Ivana Vidović Vujačić[2], Lorena Radolović Prenc[2], Mihail Poduje[3]

[1] Klinički zavod za dijagnostičku i intervencijsku radiologiju, KBC Sestre Milosrdnice, Zagreb
[2] Djelatnost za neurologiju, Opća bolnica Pula
[3] Djelatnost za radiologiju, Opća bolnica Pula

Abstract:

Aim: To present a rare case of a patient with multiple unruptured intracranial aneurysms.
Case report: A 82-year-old female patient with acute onset of headache without pain relief after taking analgesics. Non–Enhanced Multi-slice Computed Tomography (MSCT) of brain was performed and multiple vascular anomalies were suspected. Diagnostic procedures were completed with cerebral MSCT angiography which proved presence of multiple unruptured inracranial aneurysms. Aneurysms are of asymmetric localization, probably due to acquired causes and usually smaller than 10 mm.
Conclusions: This case describes patient with the biggest number of multiple unruptured intracranial aneurysms (MUIA) so far known in literature in a single patient.

Keywords: Multiple unruptured intracranial aneurysms; MSCT angiography; subarachnoid hemorrhage.

Sažetak:

Rijedak slučaj multiplih nerupturiranih intrakranijskih aneurizama
Cilj: Prezentirati rijedak slučaj pacijentice s multiplim nerupturiranim intrakranijskim aneurizmama.
Prikaz slučaja: 82-godišnja pacijentica s akutno nastalom glavoboljom bez poboljšanja na analgetsku terapiju. Na učinjenoj nativnoj višeslojnoj kompjutoriziranoj tomografiji (MSCT- Multi-slice Computed Tomography) mozga postavljena je sumnja na multiple vaskularne anomalije. Obrada je upotpunjena cerebralnom MSCT angiografijom kojom se potvrdi postojanje multiplih nerupturiranih intrakranijskih aneurizama. Aneurizme su asimetrične lokalizacije, vjerojatno posljedica stečenih uzroka i većinom manje od 10 mm.
Zaključci : Ovo je prikaz slučaja dosad najvećeg broja multiplih nerupturiranih intrakranijskih aneurizama (MUIA) poznatih u literaturi u pojedinačnog pacijenta.

Ključne riječi: Multiple nerupturirane intrakranijske aneurizme; MSCT angiografija ; subarahnoidalna hemoragija.

OPEN ACCESS

Correspondence:
Matea Prenc
mprenc@sfzg.hr

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 04 May 2023
Accepted: 04 June 2023
Published: 26 June 2023

Citation:
Prenc M, Vidović Vujačić I, Radolović Prenc L, Poduje M. A rare case of multiple unruptured intracerebral aneurysms
556=62-63 (2023): 92-96
DOI: 10.21857/mnlqgcrk8y

Introduction

Intracerebral aneurysms are pathological local expansions of the walls of cerebral arteries, caused by structural changes in the arterial wall and hemodynamic factors. About 90% of cerebral aneurysms are saccular and belong mainly to the anterior brain circulation. Only 15% of aneurysms affect the posterior cerebral circulation and are often fusiform[1]. Prevalence of unruptured intracranial aneurysms (UIA) is 5%, and the incidence of multiple aneurysms in the general population is 20-30%[2]. In the largest number of patients there are two aneurysms and up to eleven cases of UIA are described in the literature so far[3]. Multiple aneurysms are most commonly localized on the internal carotid artery (ICA) - 40%, then on the anterior communicating artery (ACoA) - 30% and about 20% on the middle cerebral artery (MCA)[1]. The largest number of aneurysms are manifested by spontaneous intracranial bleeding (90%). UIA are discovered accidentally during neuroradiological examination or are symptomatic before rupture[3].The significance of UIA treatment is best reflected in the fact that 40-60% of patients die during the first subarachnoid bleeding (SAH)[4]. In the case of multiple aneurysms, the higher probability of rupture is with those located on the vertebrobasilar junction and the posterior cerebral artery (PCA), especially if they have a larger diameter, more irregular shape and proximal localization[5]. Selection of the treatment modality depends on the patient's age, clinical condition, size and morphology of the aneurysm. The treatment of UIA still remains a controversial issue and the success of the treatment of multiple aneurysms is smaller than in the case of solitary aneurysms[6,7] .

Case report

A 82-year-old female patient was admitted to the hospital due to an acute headache without improvement on analgesic therapy. She reported already suffering from chronic headaches and hypertension. The neurological findings were normal. Results of laboratory tests including coagulogram and immunological tests were within normal limits. Non-enhanced head CT showed expansive hyperdense formations in the area of the left cavernous sinus (diameter 18 mm) and suprasellar cistern (diameter of 6 mm) (Figures 1 and 2). Multiple unruptured intracranial aneurysms (MUIA) were suspected. MSCT angiography was performed which confirmed the existence of a large aneurysm (16 x 20 x 14 mm) of the left ICA affecting the entire C3 and C4 segment (Figure 3). An aneurysm (8.6 x 4.6 x 6.1 mm) is also visible at the transition between C6 to C7 segment of the right ICA (Figure 4) and at the AcoA (6.9 x 6.9 x 6.0 mm) (Figure 5). Multiple smaller aneurysms were located at the junction of C5 and C6 segment of the left ICA, in the M1 segment of the left MCA, at the crossing point of the basilar artery to the PCA, at the crossing point of the right posterior communicating artery (PCoA) to the right P2 segment of the PCA and in the M2 segment of both MCAs. Dolichoectasia of the intracranial part of the right ICA was also seen (Figure 6). Regression of headache occurred after application of analgesic therapy and regulation of blood pressure. In consultation with the neurosurgeon, neuroradiological control was recommended prior to treatment, but due to the patient's non-agreement to endovascular treatment conservative therapy with the recommendation of further monitoring was applied.

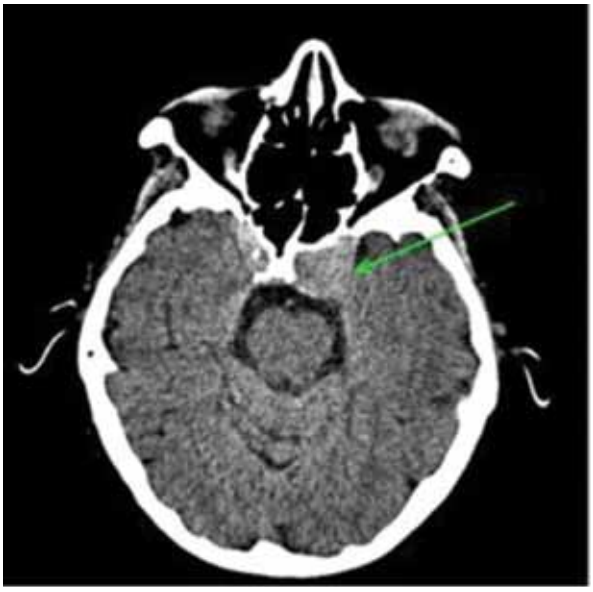


Figure 1. NECT: Hyperdense expansive lesion in the left cavernous sinus.

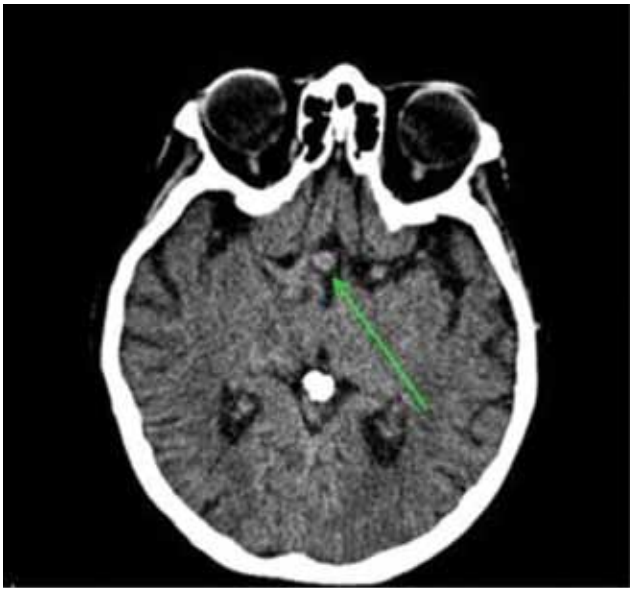
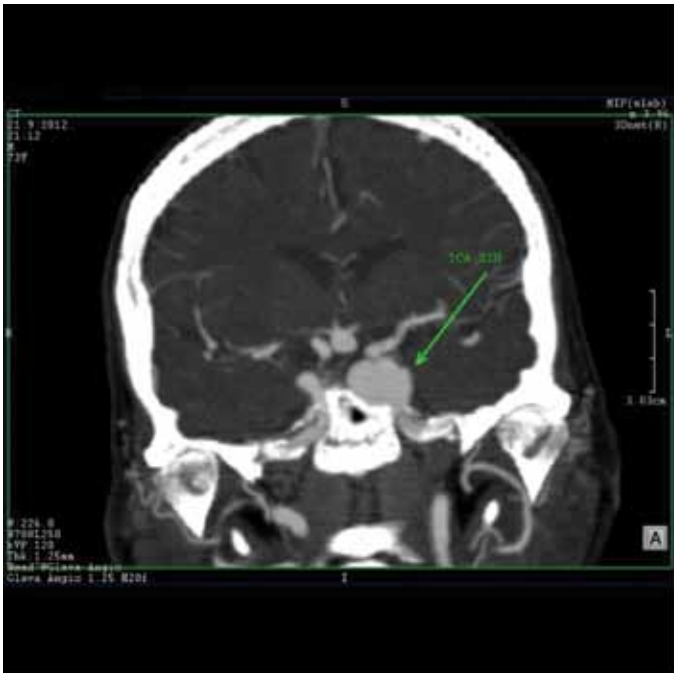


Figure 2. NECT: Expansive oval lesion in suprasellar area.



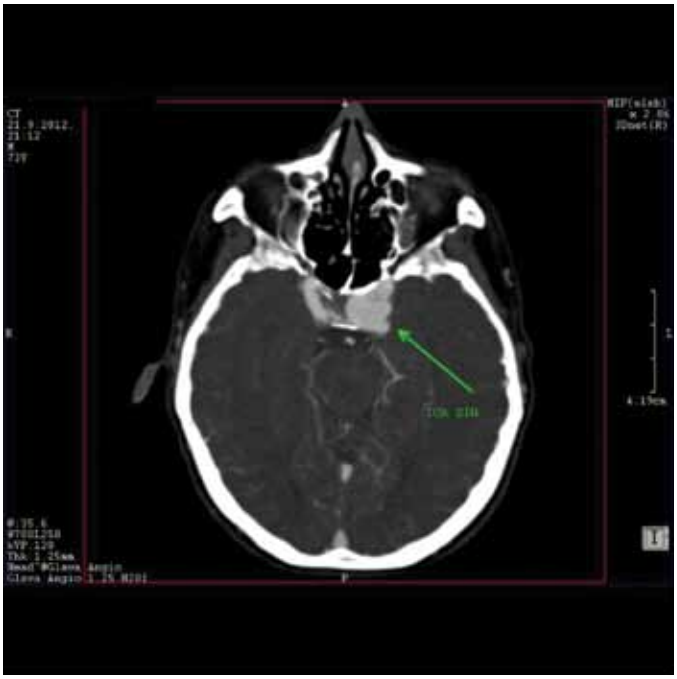


Figure 3. MSCT angiography: Aneurysm in C3 and C4 segments of the left ICA – coronal (a) and transverse (b) plane.

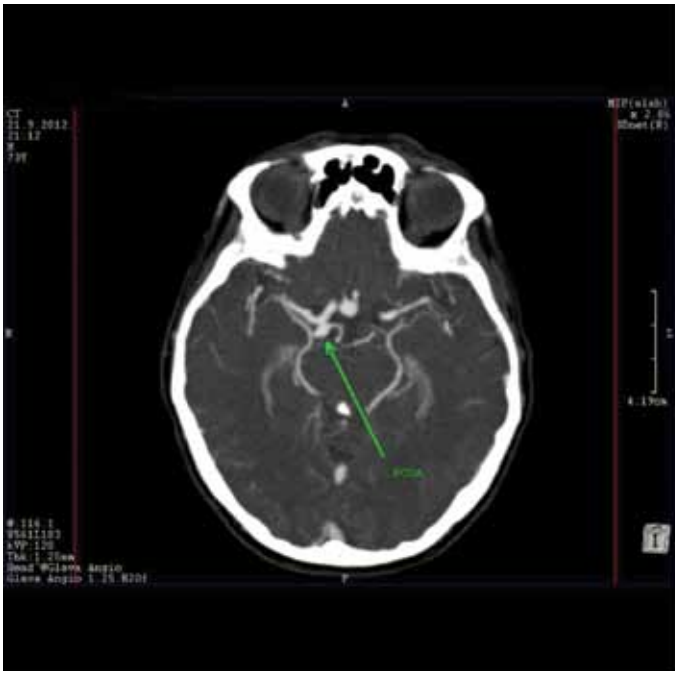


Figure 4. MSCT angiography: Aneurysm in the transition between C6 and C7 segment of the right ICA. From this aneurysm leaves the right PCoA.

Figure 5. Aneurysm of ACoA.

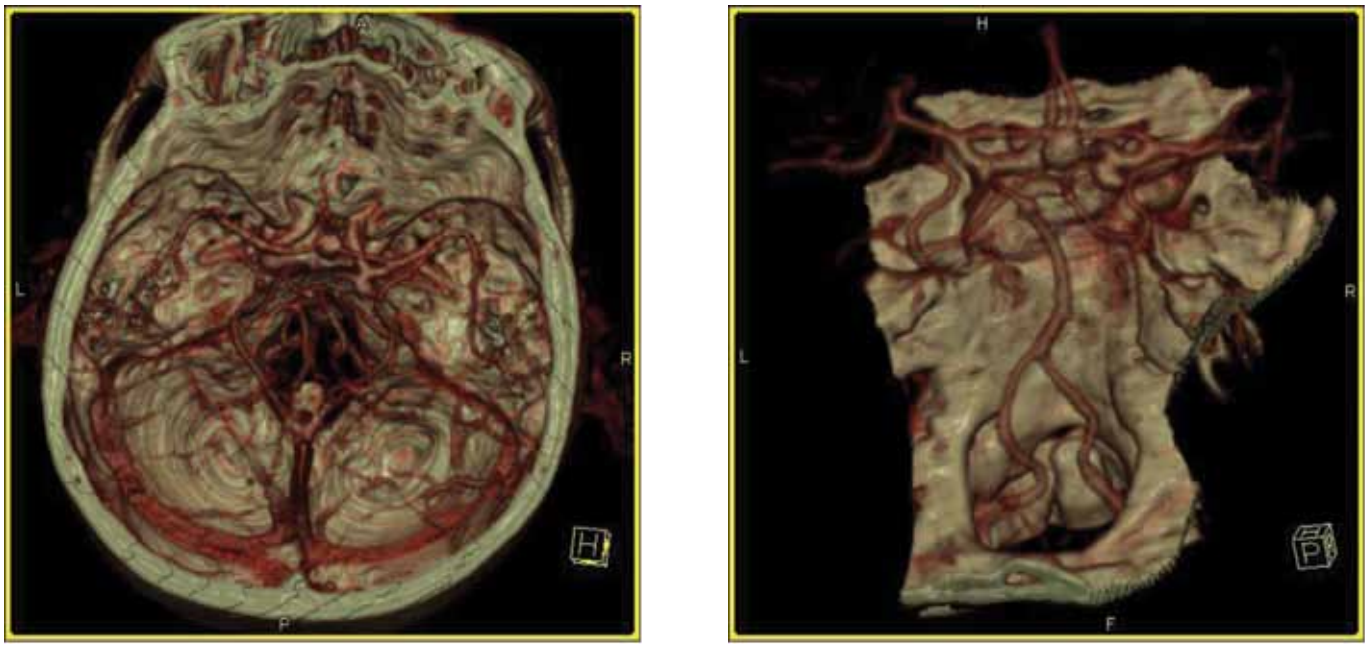


Figure 6. MSCT angiography, volume rendering: multiple intracranial aneurysms.

Discussion

MUIA occur most often on the ICA (43%) and MCA (27%). They are often linked with arterial hypertension and more frequently noted in women[2]. All of the described characteristics were manifested in our patient.

A third of pericallosal artery aneurysms are associated with aneurysm of another localization, and it is similar with the ophthalmic, anterior choroidal artery and ICA. Localization of MUIA in area PCoA is sporadic, localization in ACoA is rare and there is almost no occurrence in the basilar artery. In this case report, smaller aneurysms appeared in a rarely registered localization in the posterior circulation.

In more than 90% of MUIA cases there are two aneurysms, 3.5% of patients have three, and only 1.4% four or more aneurysms[3]. In our patient neuroradiological examination determined the existence of 13 UIA.

UIA greater than 10 mm are more likely to produce clinical symptoms before rupture. Such aneurysms are most often localized on the ICA (40-70%) and occur in middle-aged women[2]. In our patient, only one aneurysm was larger than 10 mm and it was localized on ICA. Due to the proximity of the cranial nerves it was a probable cause of neuralgic pain. More than 90% of UIA on angiography and biopsy are less than 10 mm in diameter. Prevalence of rupture is 7-15% in aneurysm with a diameter of less than 3 mm[8]. Aneurysms with a diameter of less than 10 mm have a negligible risk of rupture, and those smaller than 5 mm are complicated for invasive management[9,10].

The choice of treatment method depends on the patient's age, clinical picture, size and morphology of aneurysms. Due to the numerous risks associated with surgical treatment, brain aneurysms are a challenge, especially when they are multiple and distant from each other. Most often one larger aneurysm is symptomatic and the others are diagnosed by chance[11].

The prevailing opinion is that MUIA should be managed operatively because of the risk of later rehemorrhage (11.5% after 16 years), which is significantly higher than operative mortality for unruptured aneurysms (1%) with the usage of modern techniques. Depending on the anatomical distribution of aneurysms operative care can be performed in one or more surgical procedures. Postoperative complications are mostly ischemic, and the number of aneurysms is a risk factor for postoperative ischemia[4].

Conclusion

The number of diagnosed UIA is increasing with the development of neuroradiological imaging. Knowledge of the risk of rupture is important for the treatment decision. UIA are discovered accidentally during neuroradiological examination or when they cause neurological symptoms and outbursts . Symptomatic UIA are more common in women. When it comes to MUIA, in the majority of cases two aneurysms are confirmed in the patient, and exceptionally rarely four or more aneurysms. The largest number of MUIA described in the literature so far is 11. In this paper we reported patient with 13 aneurysms. MUIA are most often located on the ICA and MCA with asymmetric localization. They are associated with arterial hypertension and are more common in women, which is confirmed by the example from our case. Localization of MUIA in the PCoA area is sporadic, while the occurrence in the basilar artery is almost non-existent. In our patient aneurysms of those rare localizations have also been proven. MUIA are generally smaller than solitary aneurysms and in the presented case the majority were with a diameter of less than 10 mm. The success rate of surgical management of MUIA is lower than in the case of solitary aneurysms.

References

1. 1. Gavranić A., Šimić H, Škoro I et al. Subarahnoidalno krvarenje .Medicina flu minensis 2011; 47(2):143-156.
2. 2.Tae Yeon Jeon, Pyoung Jeon, Keon Ha Kim. Prevalence of unruptured intracranial aneurysm on MR angiography. Korean J Radiol 2011;12(5):547-553.
3. 3. Račić D, Kovačević M, Marinković S, Djajić V, Kovačević I, Vujović Z, Vrućinić Z. Rizik rupture i prirodni ishod nerupturisanih intrakranijumskih aneurizmi. Srpski arhiv 2002; 130:115-120.
4. 4. Roganović Z, Pavlićević G. Multiple moždane aneurizme. Vojnosanit Pregl 2002;59 (3):249-254.
5. 5. Rinkel GJ, Djibuti M, Algra A, van Gijin J. Prevalence and risk of rupture of intracranial aneurysms: a systematic review. Stroke 1998; 29:251-256.
6. 6. Rajagopal N., Yamada Y, Balaji A, Kawase T,Kato Y. Rare cases of multiple unruptured intracranial aneurysms: Illustrative report and review on management options Interdisciplinary Neurosurgery, 2019;18:1-6.
7. 7. Shen X, Xu T, Ding X, Wang W, Liu Z, Qin H. Multiple intracranial aneurysms: endovascular treatment and complications. Interv.Neuroradiol.2014;20:442-447.
8. 8. Inagawa T, Hirano A. Autopsy study of unruptured incidental intracranial aneurysms.Surg.Neurol 1990;34:361-365.
9. 9. Wiebers DO, Whisnant JP, Huston J, Meissner I, Brown RD, Piepgras DG, et al. Unruptured intracranial aneurysms: natural history, clinical outcome, and risks of surgical and andovascular treatment.Lancet 2003;362:103-110.
10. 10. Inagawa T.Surgical treatment of multiple intracranial aneurysms. Acta Neurochir 1991;108:22-9.
11. 11. Jaworska K, Dolowy J, Kusmierska M, Tomasz K, Jazwiec P. Multiple fusiform cerebral aneurysms-case report. Pol J Radiol 2012; 77(1):50-53.

Repeated intravenous thrombolytic therapy with rt-PA alteplase in treatment of early recurrent ischemic stroke

Josip Sekovanić[1,2], Sara Drnasin[1,2], Mislav Budišić[1,2], Lidija Dežmalj Grbelja[1], Marijana Bosnar Puretić[1], Marina Roje Bedeković[1,2,3]

[1] University Department of Neurology, Sestre Milosrdnice University Hospital Center, Zagreb, Croatia
[2] Faculty of Education and Rehabilitation Sciences, University of Zagreb
[3] School of Medicine, University of Zagreb

Abstract:

The 2019 year guidelines (American Heart Association / American Stroke Association – AHA/ASA) do not recommend treating recurrent acute ischemic stroke with alteplase in patients who had previous stroke in last 3 months (1,9). According to the European Stroke Organisation`s (ESO) guidelines (year 2021), there is no clear consensus. The risk of reocclusion occurs in 14-34% of patients in whom recanalisation with alteplase has been achieved (1). In this paper we present the case of our 70-year old patient with early stroke recurrence and repeated thrombolytic therapy 9 hours after the first dose of alteplase.

Keywords:

repeated thrombolytic therapy, early recurrent ischemic stroke, intravenous thrombolysis, recombinant tissue plasminogen activator, rt-PA, alteplase

Sažetak:

Ponovljena intravenozna trombolitička terapija rt-PA alteplazom u liječenju ranog recidiva moždanog udara

AHA-AHS smjernice iz 2019. godine ne preporučuju liječenje akutnog ishemijskog moždanog udara alteplazom u bolesnika koji su imali ishemijski moždani udar unatrag 3 mjeseca (1,9). Prema ESO smjernicama (2021. god.), nema jasnog konsenzusa. Rizik reokluzije se događa u 14-34% bolesnika u kojih je postignuta rekanalizacija intravenskom primjenom alteplaze (1). U ovom radu predstavljamo našeg 70-godišnjeg bolesnika s ranim recidivom ishemijskog moždanog udara te ponovljenom intravenskom trombolitičkom terapijom provedenom 9 sati nakon završetka inicijalne doze alteplaze.

Ključne riječi:

ponovljena trombolitička terapija, rani recidiv moždanog udara, intravenska tromboliza, rekombinantni tkivni plazminogen aktivator, rt-PA, alteplaza

OPEN ACCESS

Correspondence:
Josip Sekovanić
jsekovanic@gmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement:
The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 17 April 2023
Accepted: 08 June 2023
Published: 26 June 2023

Citation:
Sekovanić J, Drnasin S, Budišić M, Dežmalj Grbelja L, Bosnar Puretić M, Roje Bedeković M. Repeated intravenous thrombolytic therapy with rt-PA alteplase in treatment of early recurrent ischemic stroke
556=62-63 (2023): 98-103
DOI: 10.21857/ygjwrcp78y

Introduction

The 2019 year guidelines (AHA/ASA) do not recommend treating recurrent acute ischemic stroke with alteplase in patients who had previous stroke in last 3 months (1,9). According to the European Stroke Organisation`s (ESO) guidelines (year 2021), there is no clear consensus. According to studies, the risk of poor clinical outcome (mRS-modified Rankin Scale 3-6) was not significantly increased in these patients. Recent observational studies have not shown association of previous ischemic stroke with increased risk of intracerebral bleeding. Meta-analyses that included 52 631 patients who were treated with intravenous alteplase found no evidence of increased risk for intracerebral bleeding, death or poor functional outcome in 1.7% of patients who suffered an ischemic stroke within 3 months (1). Disadvantage of these observational studies is that they included relatively small number of patients and many studies did not report in what time period stroke recurrence occurred. Therefore it cannot be concluded in what time interval thrombolytic therapy was readministered. According to the consensus of experts, it is recommended to conduct intravenous thrombolytic therapy with alteplase in individual patients who previously had minor stroke or good clinical recovery. The risk of reocclusion occurs in 14-34% of patients in whom recanalisation with alteplase has been achieved (1). In this paper we present case of our 70-year old patient with early ischemic stroke recurrence in whom thrombolytic therapy was readministered 9 hours after initial dose of alteplase.

Case presentation

70-year old patient was admitted in primary stroke center after waking up in the night with moderately severe right arm paresis and severe paresis of his right leg (NIHSS – National Institute of Health Stroke Scale 6). He was last seen well 2 hours and 50 minutes earlier. Except arterial hypertension, the patient did not have other comorbidities (mRS 0). Emergency Multislice Computed Tomography (MSCT) of brain showed no acute lesions (Figure 1). MSCT angiography showed spasm and probable thrombus of M2 segment of the left middle cerebral artery (ACM) with suspect aneurysms up to 7 mm in M1 segment of the right ACM. The patient was transfered to the Sestre Milosrdnice University Hospital Center due to mechanical thrombectomy. During the transfer (1 hour and 40 minutes after the beginning of stroke symptoms and within the therapeutic interval of 4.5 hours, intravenous alteplase was administered. Our patient recovered to the level of moderate hemiparesis of the right extremities (NIHSS 4). Digital Subtractional Angiography was performed (Figure 2) and didn't find large vessel occlusion (LVO) or aneurysm. Eleven hours after initial neurological symptoms there was again worsening of neurological deficit in terms of right sided hemiplegia (NIHSS 9) without epileptic manifestations. Emergency DSA of the brain was performed again which again excluded LVO. Control brain MSCT scan (Figure 3) and

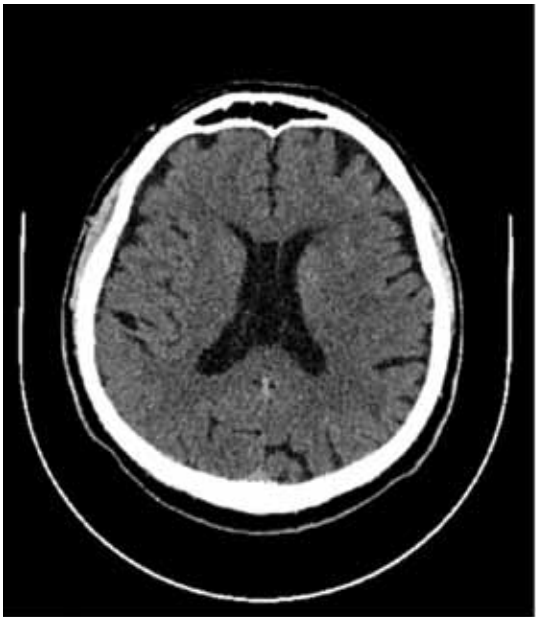


Figure 1: Brain CT before first thrombolysis

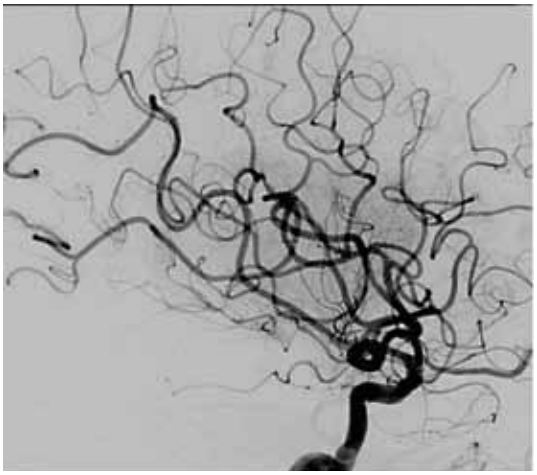


Figure 2: DSA

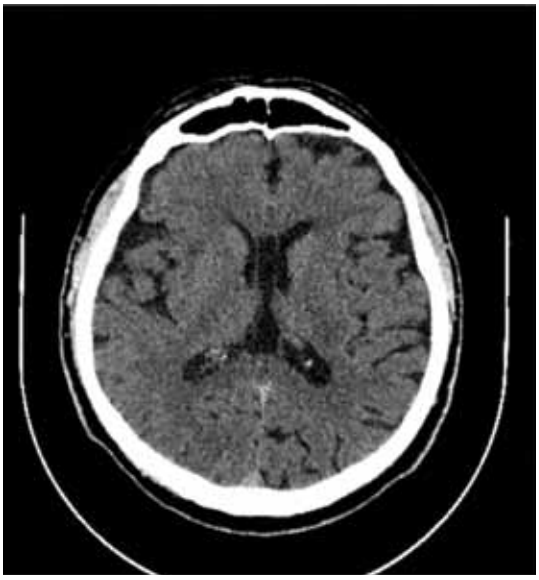


Figure 3: Brain CT after worsening

MSCT perfusion (Figure 4) showed no signs of acute ischemia with good perfusion and we have decided to readminister intravenous thrombolytic therapy (with 90 mg maximum dose of alteplase) 9 hours after the end of the first dose of rt-PA. After repeated therapy there was again clinical improvement of motor deficit to the level of mild right-sided hemiparesis (NIHSS 3). Magnetic Resonance Imaging (MRI) of brain showed a zone of fresh ischemia about 1.5 cm in diameter along the left lateral cerebral chamber and the back of the nucleus caudatus (Figures 5, 6).

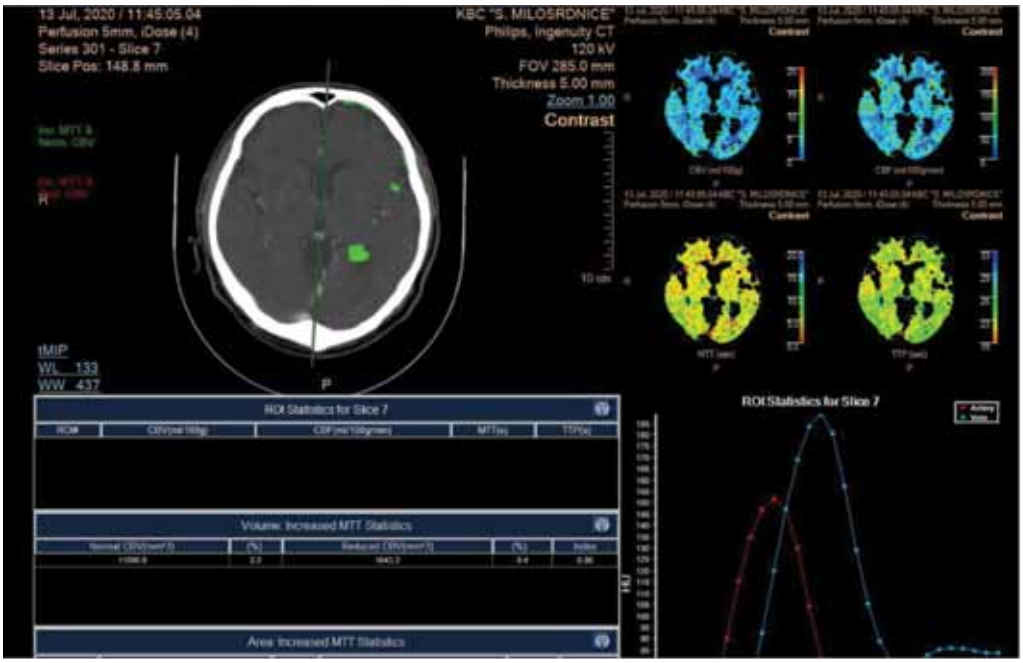


Figure 4: CT brain perfusion

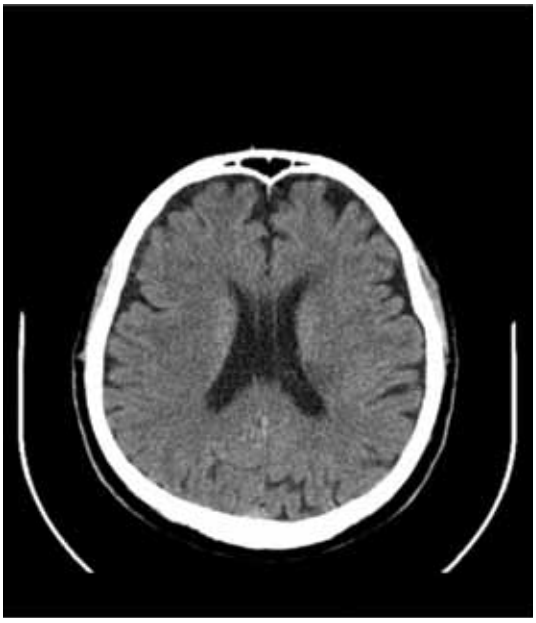


Figure 5: Control brain CT after repeated thrombolysis

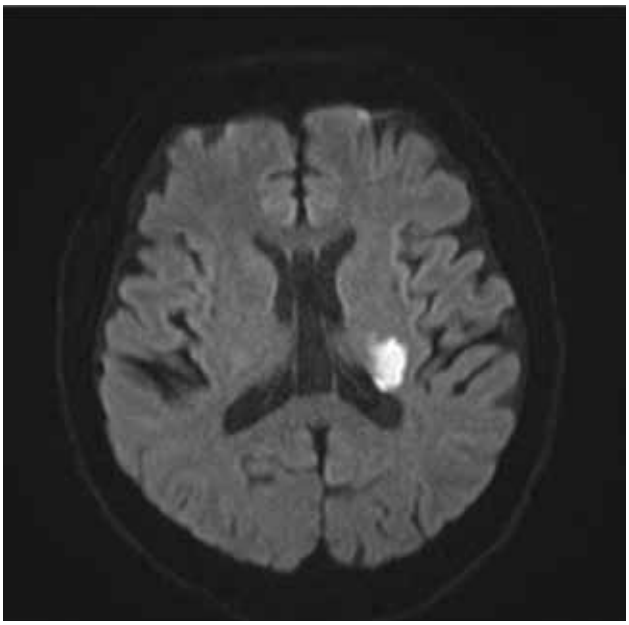


Figure 6: Brain MR after repeated thrombolysis (T2)

The early postprocedural phase was complicated with macrohematuria on the first day of hospitalization. It was stopped by rinsing the bladder, without significant decrease in red blood count. Second day of hospitalization was complicated with aggravation of inguinal hematoma at the puncture site for DSA along with swelling of the right leg and elevated D-dimers. Collor Doppler (CD) ultrasound of leg veins verified deep vein thrombosis (DVT) of the right joint femoral vein. In consultation with cardiologist, low molecular heparin was prescribed in therapeutic dose for 14 days, after which non vitamin K oral anticoagulant (NOAC) medication (rivaroxaban) was introduced. The control CD ultrasound of the leg veins showed signs of initial thrombus recanalisation, but MSCT angiography verified pseudoaneurysm of the right joint femoral artery. On 17th day of hospitalization a resection of pseudoaneurysm was performed by vascular surgeon. Days of hospitalization were additionally prolonged because of infection on the site of puncture and the need for antimicrobial therapy and active surgical treatment. Ultrasound examination of head and neck blood vessels found no significant stenosis. Holter ECG recorded no pathological rhytm. At discharge from hospital, our patient had mild right-sided hemiparesis (NIHSS 3, mRS 3-4) and neurorehabilitation was recomended.

Subsequently repeated Holter ECG recorded paroxysmal atrial fibrillation. That confirmed assumed cardioembolic etiology of a ischemic stroke and permanent anticoagulant therapy (NOAC) was continued. On following neurological controls our patient had slightly impaired fine motor skills of the right hand but he was mobile and without other neurological deficits (NIHSS 1, mRS 0).

Discussion

In this paper we have presented a patient to whom we repeated intravenous thrombolytic therapy 9 hours after the end of initial dose of rt-PA. Because of new severe neurological deficit and after the exclusion of LVO repeated rt-PA therapy was considered as the only modality of active reperfusion treatment. Readministration of intravenous alteplase after nine hours of initial dose caused no neurological deterioration. The only side effect of alteplase readministration was transitional urethrorhagia, inguinal hematoma and pseudoaneurysm as a complication of DSA and DVT. Patient was discharged from hospital with significant improvement in neurological status (NIHSS 3).

Alteplase is a thrombolytic agent that is produced by recombinant DNA technology and it was approved by United States Food and Drug Administration in 1987. Therapeutic indications are acute ischemic stroke (dose 0.9 mg/kg total to 90mg within an hour), myocardial infarction, pulmonary embolism (total doses up to 100 mg in 2-3 hours) and urological indications (3). Alteplase converts plasminogen into the proteolytic enzyme plasmin that leads to fibrinolysis and thrombus dissolution. The intravenous alteplase is metabolized through the liver with an initial half-life of 5 minutes. More than 80% of alteplase is eliminated by urine within the next 18 hours after administration (3, 4).

Repeated thrombolytic therapy with intravenous recombinant tissue plasminogen activator (rt-PA) in cases of myocardial infarction and pulmonary embolism have been shown to be safe. There are generally few patients with repeated thrombolytic therapies in acute ischemic stroke, mainly because of fear of intracerebral haemorrhage due to the damaged blood-brain barrier, existing criteria for thrombolytic therapies (1, 2, 5) and the risk of anaphylactoid reactions in repeated administration of the drug (5). Independent risk factors for hemorrhagic transformation of cerebral infarction are age, size of the infarcted region, and diabetes mellitus (12).

Topakian et al. (20) in 2005. reported first patient who succesfully received repeated intravenous rt-PA therapy for acute ischemic stroke after four days. Smadja et al. (13) reported a case of 74-year old patient with occlusion of a basilar artery. Four hours after symptom onset conventional intravenous thrombolysis (IVT) was started. After neurological deterioration (patient became unresponsive with bilateral decerebration rigiditiy), brain MRI excluded brain haemorrhage and showed progression of thrombus. Patient was given an intravenous (IV) bolus of tenecteplase 3 hours after previous rt-PA with significant improvement in neurological status after 1 hour. Han Soo Yo et al. repeated intravenous thrombolysis on 7 out of 437 patients in period from 6 days to 76 months after initial dose, with no complications and good overall outcome in 5 patient. Alhazzaa et al. (16) analyzed all thrombolysis in period from 2008. to 2012. from Ottawa Hospital, where 3 patients had repeated intravenous thrombolysis (after 6 and 70 days of initial rt-PA). 3 patients developed petechial hemorrhage within the area of subacute infarction, but all were asymptomatic with no neurological deterioration. Kahles et al. conducted a study in Germany, Switzerland and Finland on a sample of 7537 patients. There were 19 patients who received repeated intravenous thrombolysis. The median age of these patients was 68±12 years, 37% were women, the median interval between thrombolysis was 30 days (minimum 13, maximum 50 days). Clinical improvement was achieved in 79% of patients and there were no intracranial bleeding. They concluded that patients with small areas of infarct after the initial stroke (medium size about 1.5 cm^3) can be considered for repeated thrombolytic therapy within 3 months (17). Capellari et al. (18) retrospectively reviewed the medical records of stroke patients who repeated intravenous infusion of alteplase after recurrent stroke from among the 615 consecutive stroke patients admitted to Stroke Unit Verona General Hospital, from December 2004 to September 2013. In 27 patients repeated iv thrombolytic treatment was administered once after recurrent stroke and in 3 patients twice. IV thrombolytic procedures were repeated from second day

after the initial dose to 5 years after first IV thrombolysis. They concluded that re-thrombolysis may be safe and effective when recurrent stroke occurs after a period of complete neurologic regression lasting at least 24 hours or minor disability (mRS score ≤2) lasting at least 3 months since the previous stroke. Šupe et al. (8) presented 53-year old patient with occlusion and reocclusion of basilar artery where re-thrombolytic therapy was administered after 54 hours followed by repeated mechanical thrombectomy. Sposato et al. (19) presented a 76-year old woman with known paroxysmal atrial fibrillation who was admitted because of an acute right middle cerebral artery ischemic stroke and who underwent repeated systemic thrombolysis within 110 hours. A hemorrhagic transformation of the left middle cerebral artery infarction was noted on follow-up cranial MSCT scans. The patient did not recover from the second cerebrovascular event and died 25 days after admission.

Time for repeated thrombolytic therapy from available studies varies from 48 hours to several years, but there is no significant number of intracerebral bleeding or allergic reactions (5, 6, 7, 8, 10, 11). Less satisfactory recovery was observed after the second dose of thrombolytic therapy than after the initial dose, probably as a result of previous lesion of cerebral parenchyma.

Conclusion

In summary, there is no clear expert consensus for repeated intravenous thrombolytic therapy with alteplase in patients with early cerebral infarction recurrence. From the available literature, at the time of writing this case, we found only one case report where intravenous thrombolytic therapy was repeated after 3 hours in patient with basilar artery occlusion after the initial dose of intravenous rt-PA tenecteplase was administered (13). We presented a case of our 70-year old patient with early ischemic stroke recurrence in whom thrombolytic therapy was readministered 9 hours after initial dose of alteplase with a good clinical outcome. This review speaks in favor of the safety and efficacy of administration of repeated intravenous thrombolytic therapy in thoroughly selected early ischemic stroke recurrence patients and the need for possible further reevaluation of excluding criteria in treatment of acute ischemic stroke with alteplase. The main predictor of intracerebral bleeding could be a severity of the initial neurological deficit and previous neurological damage. Further clinical trials and patient registers are needed.

References:

1. Powers, W., Rabinstein A. etal: Guidelines for theEarly Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for theEarly Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American StrokeAssociation . Available at https://doi.org/10.1161/STR.0000000000000211.
2. Eivind Berge, William Whiteley e tal.: European StrokeOrganisation (ESO) guidelines on intravenous thrombolysis for acute ischemic stroke**.** Available at https://doi.org/10.1177/23969873219898
3. Mirembe Reed; Connor C. Kerndt; Diala Nicolas. Alteplase - StatPearls - NCBI Bookshelf (nih.gov). Available at https://www.ncbi.nlm.nih.gov/books/NBK499977
4. Drugbank online. Available at https://go.drugbank.com/drugs/DB00009
5. Fugate JE, Rabinstein AA. Absolute and relative contraindications to IV rt-PA for acute ischemic stroke. Neurohospitalist. 2015; 5: 110-12, DOI: 10.1177/1941874415578532
6. Yoo HS, Kim YD, Lee HS, Song D, Song TJ, Kim BM, etal. Repeated thrombolytic therapy in patients with recurrent acute ischemic stroke. J Stroke. 2013; 15: 182-188, DOI: 10.5853/jos.2013.15.3.182
7. Wu C, Wu D, Chen J, Li C, Ji H. Why not Intravenous Thrombolysis in patients with recurrent stroke within 3 Months? AgingDis. 2018; DOI: 10.14336/AD.2017.0406
8. Svjetlana Š, Nikola B, Zdravka P, David O, Josip L, et al. (2020) Safety of Repeated Reperfusion Therapy (Thrombolysis and Trombectomy) in Early Recurrent Stroke: A Case Report. J Neurol Disord Stroke 7(3): 1166.
9. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. Cochrane DatabaseSystRev. 2014; Available at https://doi.org/10.1002/14651858.CD000213.pub3
10. Mona Laible a Ekkehardt Jenetzky, Markus Möhlenbruch, Peter Arthur Ringleb. Repeated Intravenous Treatment with Recombinant Tissue - Type Plasminogen Activator in Patients with Acute Ischemic Stroke, Eur Neurol 2015;74:127–134, DOI: 10.1159/000439048
11. Heldner MR, Mattle HP, Jung S, Fischer U, Gralla J, Zubler C, et al.Thrombolysis in patients with prior stroke within the last 3 months.Eur J Neurol. 2014; 21: 1493-1499, DOI: 10.1111/ene.12519
12. L. Kerenyi, L. Kardos, J. Szász,S. Szatmári, D. Bereczki,K. Hegedüs,L. Csiba Factors influencing hemorrhagic transformation in ischemic stroke: a clinicopathological comparison. Available at https://doi.org/10.1111/j.1468-1331.2006.01489.x

13. Smadja, D., Olindo, S., Saint-Vil, M., & Chausson, N. (2009). Sequential Combination of Two Intravenous Thrombolytics (Recombinant Tissue Plasminogen Activator/ Tenecteplase) in a Patient with Stroke and Cardioembolic Basilar Artery Occlusion. Journal of Stroke and Cerebrovascular Diseases, 18(1), 68–71.
14. Jian Wu, Qiang Huang, Qing-feng Ma: What Matters in the Results of Repeated Intravenous Thrombolysis for Recurrent Ischemic Stroke? Eur Neurol 2016;75:150–154, DOI: 10.1159/000444481
15. Robert Joseph Cruz Sarmiento , Jose Danilo Bengzon Diestro , Adrian Isidoro Espiritu , Maria Cristina Zarsadias San Jose Safety and Efficacy of Repeated Thrombolysis with Alteplase in Early Recurrent Ischemic Stroke: A Systematic Review, J Stroke Cerebrovasc Dis, . 2019 Oct;28(10):104290, DOI: 10.1016/j.jstrokecerebrovasdis.2019.07.006
16. Alhazzaa M, Sharma M, Blacquiere D, Stotts G, Hogan M, Dowlatshahi D (2013). Thrombolysis despite recent stroke: a case series. Stroke, 44: 1736-8.
17. Timo Kahles et al., Repeated Intravenous Thrombolysis for Early Recurrent Stroke, Challenging the Exclusion Criteri-onse, Stroke. 2016;47:2133–2135, Available at https://doi.org/10.1161/STROKEAHA.116.013599
18. Cappellari M, Moretto G, Bovi P (2014). Repeated intravenous thrombolysis after recurrent stroke. A case series and review of the literature. J Neurol Sci, 345: 181-3.
19. Sposato LA, Salutto V, Beratti DE, et al. Adverse outcome of early recurrent ischemic stroke secondary to atrial fibrillation after repeated systemic thrombolysis. Vasc Med 2013;2013.
20. Topakian R, Gruber F, Fellner FA, et al. Thrombolysis beyond the guidelines: two treatments in one subject within 90 hours based on a modified magnetic resonance imaging brain clock concept. Stroke 2005;36: e162-e164.

Abbreviatons:

AHA / ASA – American Heart Association / American Stroke Associtation
ESO – European Stroke Organisation
mRS – modified Rankin Scale
NIHSS – National Institute of Health Stroke Scale
MSCT – Multislice Computed Tomography
ACM – middle cerebral artery
IVT – intravenous thrombolysis
IV - intravenous
DSA – Digital Subtraction Angiography
LVO – large vessel occlusion
MRI – Magnetic resonance imaging
CD ultrasound– Color Doppler ultrasound
DVT – Deep Vein Thrombosis
NOAC – non vitamin K oral anticoagulant
rt-PA – recombinant tissue- plasminogen activator
FDA – Food and Drug Administration

Secondary central nervous system involvement in systemic ALK+ anaplastic large cell lymphoma: a case report

Žana Besser Silconi[*1], Biljana Jelić Puškarić[2], Frederic-Ivan Silconi[3], Dražen Perić[4]

[1] Department of Pathology and Cytology, Pula General Hospital, Pula, Croatia
[2] Department of Pathology and Cytology, Merkur University Hospital, Zagreb, Croatia
[3] Department of Neurology, Pula General Hospital, Pula, Croatia
[4] Department of Radiology, Pula General Hospital, Pula, Croatia

Abstract:

Systemic anaplastic large cell lymphoma is an infrequent form of non-Hodgkin lymphoma determined by the expression of CD30 with different clinical characteristics in its presentation. The majority of patients with anaplastic large cell lymphoma are in an advanced stage of the disease at the time of diagnosis but rarely with a leptomeningeal or central nervous system infiltration. We have presented a young patient with widespread systemic ALK+ anaplastic large cell lymphoma and a secondary central nervous system involvement verified by cytologic examination of the cerebrospinal fluid.

Keywords: anaplastic large cell lymphoma, central nervous system, cerebrospinal fluid, cytology.

Sažetak:

Sekundarna zahvaćenost središnjeg živčanog sustava kod sistemskog ALK+ anaplastičnog velikostaničnog limfoma: prikaz slučaja

Sistemski anaplastični limfom velikih stanica je rijedak oblik ne-Hodgkinovog limfoma determiniran ekspresijom CD30 s različitim kliničkim karakteristikama u svojoj prezentaciji. Većina bolesnika s anaplastičnim limfomom velikih stanica je u uznapredovalom stadiju bolesti u vrijeme postavljanja dijagnoze, ali rijetko s infiltracijom leptomeningea ili središnjeg živčanog sustava. Prikazali smo mladog bolesnika s raširenim sistemskim ALK+ anaplastičnim velikostaničnim limfomom i sekundarnom zahvaćenošću središnjeg živčanog sustava potvrđenom citološkim pregledom cerebrospinalne tekućine.

Ključne riječi: anaplastični velikostanični limfom, središnji živčani sustav, cerebrospinalna tekućina, citologija.

OPEN ACCESS

Correspondence:
Žana Besser Silconi
zbsilconi@gmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 23 May 2023
Accepted: 08 June 2023
Published: 26 June 2023

Citation:
Besser Silconi Ž, Jelić Puškarić B, Silconi F-I, Perić D. Secondary central nervous system involvement in systemic ALK+ anaplastic large cell lymphoma: a case report
556=62-63 (2023): 104-109
DOI: 10.21857/y26kecl569

Introduction

Anaplastic large cell lymphoma (ALCL) named "Ki-1 positive lymphoma" was first described in 1985 by Stein and colleagues as a subset of non-Hodgkin lymphomas (NHLs) with large CD30 (Ki-1) positive anaplastic cells, which cohesively expand and occupied lymph node sinuses (1). As a distinct clinicopathologic subtype of NHLs, ALCL is placed in the revised World Health Organization (WHO) Classification of tumours of hematopoietic and lymphoid tissues. By the definition, "ALK-positive (ALK+) anaplastic large cell lymphoma (ALCL) is a T-cell lymphoma consisting of lymphoid cells that are usually large and have abundant cytoplasm and pleomorphic, often horseshoe-shaped nuclei, with a chromosomal translocation involving the ALK gene and expression of ALK protein and CD30" (2:413). ALK+ ALCL accounts for approximately 3% of adult non-Hodgkin lymphomas and 10-20% of childhood lymphomas; it is most common in the first three decades of life. There is a male predominance in ALK+ ALCL with a male-to-female ratio of 1.5:1 (2). It shows an aggressive behavior with rapidly progressive adenopathy and systemic symptoms especially fever, profuse night sweats, and weight loss.

Currently, four different ALCL entities are recognized in the 2016 WHO classification: systemic ALCL ALK(+), systemic ALCL ALK(–), primary cutaneous ALCL, and breast implant-associated ALCL. ALK(+) ALCL exhibits a wide spectrum of cell morphology ranging from small to large and pleomorphic lymphoma cells, so based on that, there are five morphologic patterns of ALK+ ALCL: common (the most frequent morphological variant), lymphohistiocytic, small cell, Hodgkin-like, and composite pattern. The sheets of large lymphoid cells featuring "hallmark" cells are seen in histological and cytological samples of most patients with the common type of ALCL (3). ALK(+) ALCL has ALK gene rearrangements and infers a better prognosis compared with ALK(-) ALCL but unfortunately, at the time of diagnosis, most patients are in an advanced stage of the disease (III–IV stage) (4).

The reports of systemic ALCL with central nervous system (CNS) involvement are sporadic and diagnosing is sometimes very challenging. The CNS can be affected either at initial diagnosis or letter as a relapse and "secondary CNS T-cell lymphoma" is considered in both forms (5). The prognosis is unfavorable so it is necessary to detect that kind of lymphoma metastasizing as soon as possible with the teamwork of clinicians, neuroradiologists, and cytopathologists.

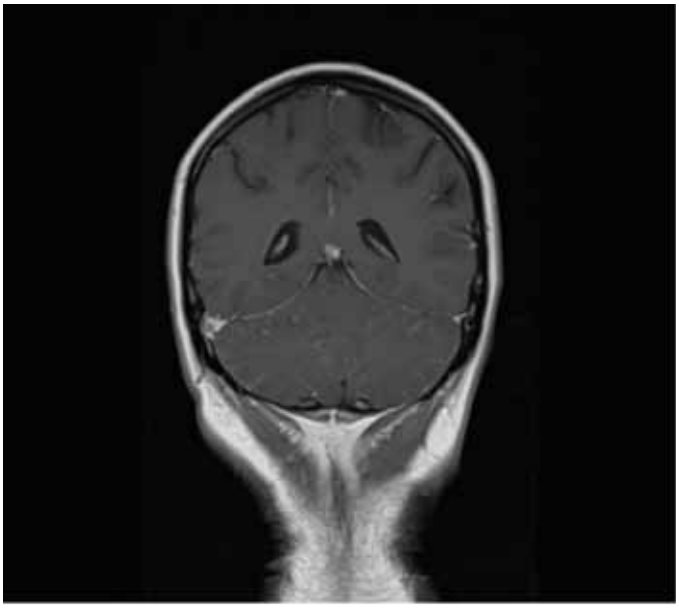
Case Presentation

A 39-year-old woman presented with pain and a lump in the right inguinal region with an on-and-off fever for one month. Ultrasound examination of both inguinal regions revealed enlarged pathological lymph nodes in conglomerates. Contrast-enhanced Computed Tomography (CT) of the thorax and abdomen revealed enlarged bilateral cervical, axillary, mediastinal, retroperitoneal, and inguinal lymph nodes along with mild hepatomegaly and moderate bilateral pleural effusions. After a hematological examination, the cervical node biopsy was performed. Pathohistological findings revealed a total replacement of architecture by a population of large polymorph atypical lymphoid cells, immunohistochemically stained positive with CD30, CD4, CD7, and ALK, so the diagnosis of ALK+ anaplastic large cell lymphoma (common type) was confirmed. The proliferative index Ki 67 was 90%. The bone marrow and peripheral blood examination did not reveal any tumour infiltration. The patient received induction chemotherapy CHOEPx1 and BV-CHEPx1. After one cycle of chemotherapy, the patient complained of severe headaches and vomiting for a few days. A neurological examination followed by contrast-enhanced CT of the brain did not show any significant intracranial pathology.

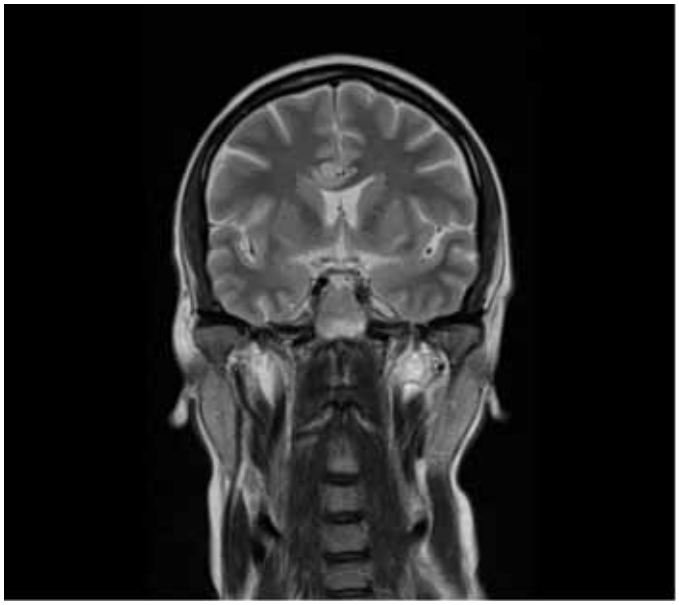
Because of permanent headache, brain Magnetic Resonance Imaging (MRI) was performed (Figure 1), which showed in the ventral part area of the cingulate gyrus on the right side, corticosubcortically a visible T2 and FLAIR elevated signal, in an area of 13 mm, with the involvement of the corpus callosum where the elevated signal discreetly crosses the central line to the left. Only the cingulate portion up to 8 mm in size showed a post-contrast enhancement, while the signal increase in the corpus callosum is not enhanced by contrast. Also, the cingulate part shows quite discrete diffusion restriction centrally. Discrete post-contrast enhancement is also visible superficially in the sulci next to the cingulate gyrus bilaterally, as a leptomeningeal involvement. Leptomeningeal enhancement is seen also in basal sulci supratentorial and most of the sulci infratentorial, so a secondary CNS lymphoma is therefore considered, and cerebrospinal fluid (CSF) examination was advised.

CSF sampling was obtained to determine levels of protein, glucose, and lactate, cell counts as well cytological analysis. Our patient's CSF sample was slightly cloudy, and xanthochromic; biochemical measurements showed elevated protein (3.32 g/L) and lactate (5.88 mmol/L) levels, and decreased glucose level (1.2 mmol/L) with increased total leukocyte ($80x10^6$/L), and erythrocytes ($3000x10^6$/L) count. The cytocentrifuge preparation of the remaining CSF specimens showed large atypical lymphoid cells with marked pleomorphism and nuclear irregularity, immunocytochemically stained positive with CD30, CD7, and ALK partially as proof of infiltration by ALCL cells (Figure 2). In this case, cytomorphology and immunocytochemical analyses of CSF confirm the presence of anaplastic lymphatic cells.

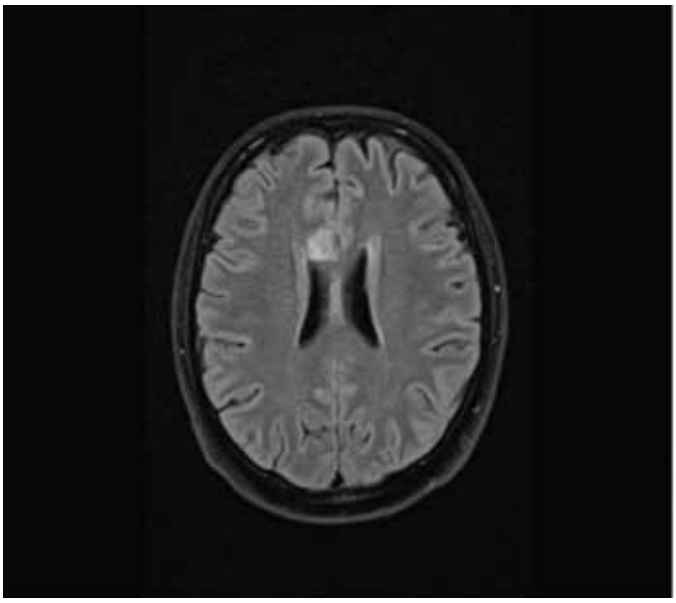
During the next two weeks after the diagnosis of CNS involvement by anaplastic lymphoma cells was established, despite the therapy, the patient's condition substantially worsened leading to a lethal outcome.



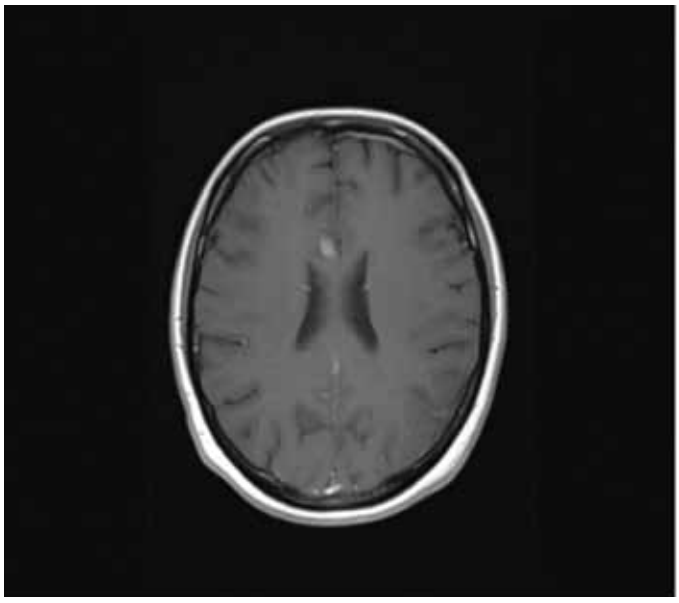
A.



B.

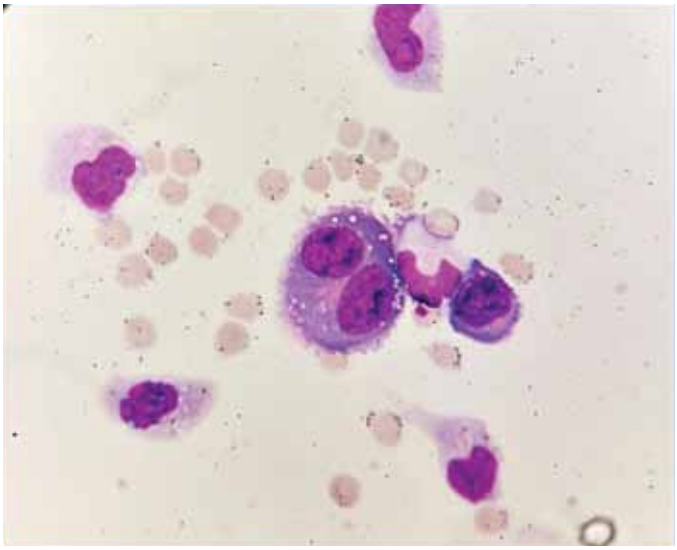


C.

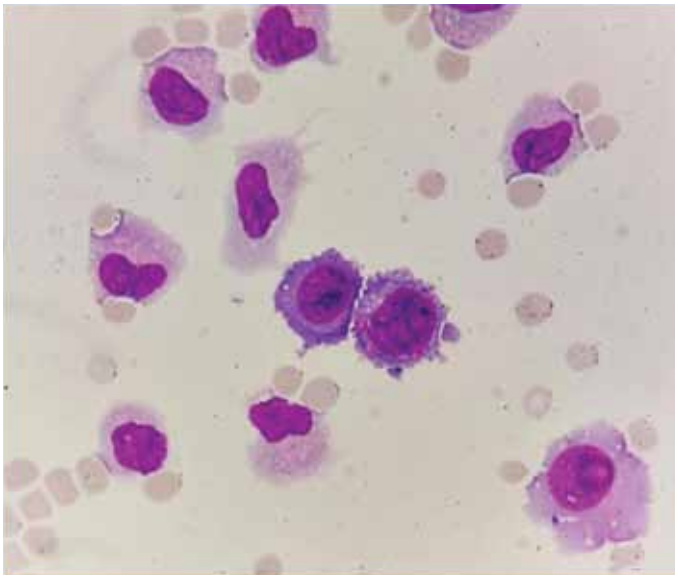


D.

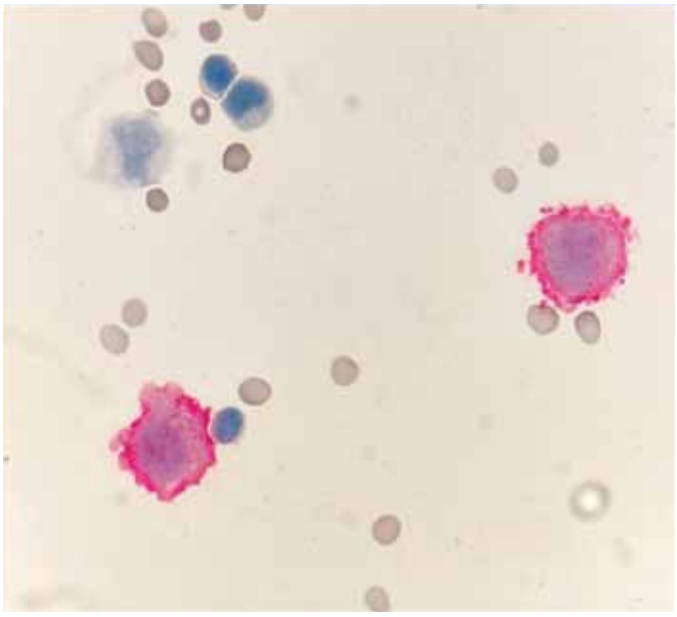
Figure 1. A) T1 postcontrast coronal plane shows leptomeningeal enhancement in basal sulci, supratentorial, and most of the sulci infratentorial; B) T2 coronal plane without contrast shows hyperintense areal in the cingulate gyrus on the right side and in the corpus callosum where it crosses the midline to the left; C) On axial T2 scan hyperintense lesion is seen in the right cingulate gyrus; D) On postcontrast T1 axial scan only the central portion of the lesion shows enhancement.



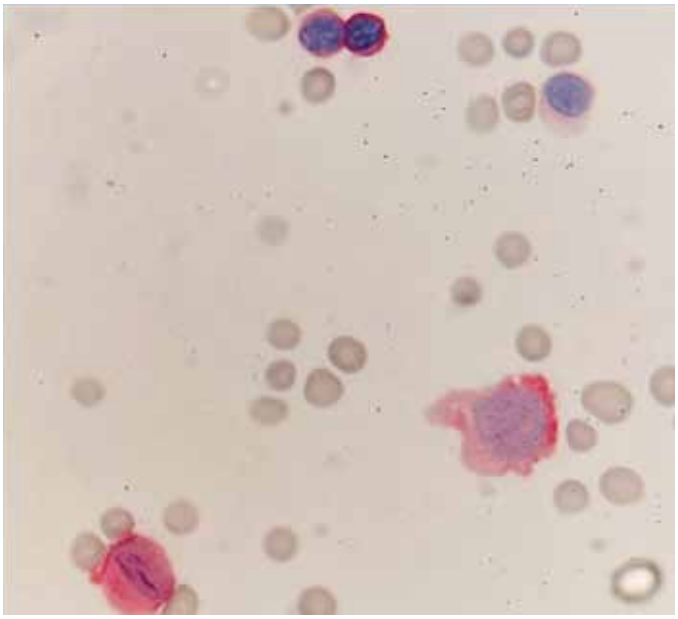
A.



B.



C.



D.

Figure 2. A-B) Large atypical lymphatic cells in the cerebrospinal fluid sediment of a patient with anaplastic large cell lymphoma, MGG stain, x1000; C) CD30 positive cells in the cerebrospinal fluid sediment of a patient with anaplastic large cell lymphoma, immunocytochemistry, LSAB, x1000; D) CD7 positive cells in the CSF sediment of a patient with anaplastic large cell lymphoma, immunocytochemistry, LSAB, x1000.

Discussion

The reports of systemic ALCL with involvement of the central nervous system (CNS) are very occasional. Most cases reported in the world's literature are primary central nervous system ALCLs. CNS can be affected either at initial diagnosis or at recurrence, and both forms are considered "secondary CNS T-cell lymphoma" (5). Systemic ALCL is primarily a nodal disease, however, extranodal involvement is seen in ~20% of cases, most often involving skin, liver, soft tissues, bone, and bone marrow (7). The primary and secondary sites of the lymphoma can appear in almost any location so physicians should keep oncological alertness. The infiltration of the central nervous system is accompanied by various neurological disorders such as nausea, vomiting, neck stiffness, persistent headaches, diplopia or other visual impairments, different level of cognitive decline, disorientation regarding the time and place, and consciousness level impairment (8). Neuroimaging shows good diagnostic sensitivity but low specificity for distinguishing secondary CNS T-cell lymphomas. Brain CT is usually the first imaging tool due to its availability, however, brain MRI is the method of choice for better investigation of patients with lymphoma (5). Involvement of the CSF in such cases is even more uncommon. CSF cytology and immunocytochemical analyses may help confirm tumour cell presence (6). Detection of atypical lymphoid cells in CSF indicates CNS infiltration in ALCL and brings immeasurably significance both from a prognostic and therapeutic point of view (9). Involvement of the CNS is rare and often associated with a poor prognosis (2). The literature about secondary CNS T-cell lymphoma is sparse, and primarily constituted by single case reports and small case series due to low incidence of this malignancy. However, reported studies similarly suggest high mortality rates related to this unfavorable event (5).
Multiple factors can affect the adverse clinical outcomes of patients with secondary CNS ALCL, including negative ALK expression, monomorphic neoplastic cells, amount of tumour necrosis, multifocal systemic spreading, leukemic phase, size and location of the tumour in the CNS, and other factors such as acute encephalopathy, additional cytogenetic aberrations, and resistance to chemotherapy (10).

Conclusion

Involvement of the central nervous system by systemic anaplastic large cell lymphoma is uncommon but results in an adverse prognosis, therefore prompt examinations are necessary to confirm this type of malignant spreading as early as possible for a more successful treatment. Our case report emphasizes the importance of cerebrospinal fluid cytology in a lymphoma patient with neurologic symptoms for rapid and accurate diagnosis.

References

1. Stein H, Mason DY, Gerdes J, O'Connor N, Wainscoat J, Pallesen G, Gatter K, Falini B, Delsol G, Lemke H, et al. The expression of the Hodgkin's disease associated antigen Ki-1 in reactive and neoplastic lymphoid tissue: evidence that Reed-Sternberg cells and histiocytic malignancies are derived from activated lymphoid cells. Blood. 1985 Oct;66(4):848-58. PMID: 3876124.
2. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues. Fourth Edition; 2017; p 413-422.
3. Stein H, Foss HD, Dürkop H, Marafioti T, Delsol G, Pulford K, Pileri S, Falini B. CD30(+) anaplastic large cell lymphoma: a review of its histopathologic, genetic, and clinical features. Blood. 2000 Dec 1;96(12):3681-95. PMID: 11090048.
4. Montes-Mojarro IA, Steinhilber J, Bonzheim I, Quintanilla-Martinez L, Fend F. The Pathological Spectrum of Systemic Anaplastic Large Cell Lymphoma (ALCL). Cancers (Basel). 2018 Apr 4;10(4):107. doi: 10.3390/cancers10040107. PMID: 29617304; PMCID: PMC5923362.
5. Zing N, Fischer T, Federico M, Chiattone C, Ferreri AJM. Diagnosis, prevention and treatment of central nervous system involvement in peripheral t-cell lymphomas. Crit Rev Oncol Hematol. 2021 Nov;167:103496. doi: 10.1016/j.critrevonc.2021.103496. Epub 2021 Oct 12. PMID: 34653598.
6. Roth P, Weller M. Management of neoplastic meningitis. Chin Clin Oncol. 2015 Jun;4(2):26. doi: 10.3978/j.issn.2304-3865.2015.05.02. PMID: 26112812.
7. Falini B, Pileri S, Zinzani PL, Carbone A, Zagonel V, Wolf-Peeters C, Verhoef G, Menestrina F, Todeschini G, Paulli M, Lazzarino M, Giardini R, Aiello A, Foss HD, Araujo I, Fizzotti M, Pelicci PG, Flenghi L, Martelli MF, Santucci A. ALK+ lymphoma: clinico-pathological findings and outcome. Blood. 1999 Apr 15;93(8):2697-706. PMID: 10194450.
8. Pogorzały B, Kurzawa P, Mielniczek G, Dopierała M, Singh S, Derwich K. The Diagnostic Difficulties and The Delayed Identification of Anaplastic Large Cell Lymphoma in A Teenage Patient. A Review of Literature. Biomed J Sci Tech Res. 2021;37(5):29844-50. doi: 10.26717/BJSTR.2021.37.006067
9. Dehuri P, Bhandary C, Gochhait D, Srinivas BH, Basu D, Siddaraju N. Cytology of cerebrospinal fluid involvement in systemic anaplastic large-cell lymphoma. Cytopathology. 2018 Jun;29(3):303-305. doi: 10.1111/cyt.12522. Epub 2018 Feb 19. PMID: 29457294.
10. Zhang X, Bui MM, Caracciolo J, Field TL, Zhang L. Adult anaplastic large cell lymphoma involving the central nervous system: a rare clinical scenario. Ann Hematol. 2011 Jun;90(6):721-3. doi: 10.1007/s00277-010-1074-2. Epub 2010 Sep 14. PMID: 20838823.

Long waiting lists cause a "Vertigo Issue" many health care systems – from Croatian perspective

Filip Đerke[1,2], Slaven Lasić[1], Jasna Badžak[1], Vida Demarin[3]

[1] Department of Neurology, University Hospital Dubrava, Zagreb, Croatia
[2] Department of Psychiatry and Neurology, Faculty of Dental Medicine and Health, JJ Strossmayer University of Osijek, Osijek, Croatia
[3] International Institute for Brain Health, Zagreb, Croatia

OPEN ACCESS

Correspondence:
Filip Đerke
filip@mozak.hr

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 27 February 2023
Accepted: 15 May 2023
Published: 26 June 2023

Citation:
Đerke F, Lasić S, Badžak J, Demarin V. Long waiting lists cause a "Vertigo Issue" many health care systems – from Croatian perspective
556=62-63 (2023): 110-112
DOI: 10.21857/94kl4cl3om

After headache, vertigo is the most common symptom, not only in neurology or otorhinolaryngology but also one of the most common symptoms in medicine in general. Due to the different aetiology, acute and chronic manifestations, combination with other diseases, drugs, or other substances such as narcotics, alcohol or synthetic drugs, and unclear description of vertiginous symptoms on admission, vertigo as a disease or only a symptom can easily mislead. Due to the illusiveness of the symptoms as perceived and reported by patients and doctors alike, vertiginous symptoms warrant cooperation between patients and doctors, and amongst doctors of different specialities as well. In the Republic of Croatia, as well as in the rest of Europe[1], the waiting lists for an appointment in the hospital are getting longer and longer. Moreover, it can take several months to a year to get an appointment with a specialist.

Waiting lists

The waiting list for hospitals for vertigo can vary depending on several factors, such as the healthcare system in a particular country or region, the availability of specialized healthcare providers, and the severity of the condition. In general, the waiting times for treatment of vertigo can range from a few weeks to several months. This is because there may be a limited number of healthcare professionals who specialize in treating vertigo, such as otolaryngologists or neurologists. Additionally, diagnostic tests, such as vestibular function tests or imaging studies, may also contribute to the waiting time. There can be several issues associated with waiting lists for vertigo treatment. Some common challenges include:

a) Limited resources: Hospitals and healthcare facilities may have a limited number of specialists, equipment, and resources dedicated to diagnosing and treating vertigo. This can result in longer waiting times for patients seeking treatment.
b) High demand: Vertigo is a common symptom, and many individuals may seek medical attention for its treatment. The high demand for services can contribute to longer waiting lists.
c) Prioritization of cases: Hospitals often prioritize patients based on the severity of their condition. Patients with more severe or urgent cases may be given priority over those with less urgent cases. This can lead to longer waiting times for individuals with milder or less urgent symptoms.
d) Geographic location: The availability of specialized healthcare providers can vary depending on the geographic location. Individuals residing in rural or remote areas may have limited access to healthcare services, resulting in longer waiting times.

[1] https://www.theguardian.com/society/2023/feb/08/nhs-waiting-lists-in-england-unlikely-to-fall-in-2023-research-suggests

To mitigate these issues, healthcare systems can implement strategies such as increasing the number of specialists, improving access to diagnostic tests, and streamlining referral processes. Additionally, telemedicine or virtual consultations can also help reduce waiting times by providing remote access to healthcare professionals.

Role of family physicians

Family doctors can play an essential role in helping patients with vertigo. Here are some ways they can assist:

a) Initial assessment and diagnosis: When a patient presents with symptoms of vertigo, a family doctor can conduct a comprehensive medical history and physical examination. They can evaluate the duration, frequency, and triggers of vertigo episodes and identify any accompanying symptoms. This assessment helps in determining the potential causes of vertigo and ruling out other underlying conditions.
b) Treatment and management: In many cases, family doctors can initiate treatment for common causes of vertigo, such as benign paroxysmal positional vertigo (BPPV). They may perform specific maneuvers, like the Epley maneuver, to reposition displaced particles in the inner ear and alleviate symptoms. Family doctors can also prescribe medications to manage symptoms, such as anti-nausea medications or vestibular suppressants.
c) Referral to specialists: If the vertigo persists or is caused by a more complex underlying condition, family doctors can refer patients to appropriate specialists, such as otolaryngologists or neurologists. These specialists can provide further evaluation, advanced diagnostic tests, and specialized treatments.
d) Follow-up and monitoring: Family doctors can follow up with patients after initial treatment or referral to assess the effectiveness of interventions and adjust as necessary. They can monitor the patient's progress, provide guidance on self-care strategies, and address any concerns or complications that may arise during treatment.
e) Patient education: Family doctors can educate patients about vertigo, its causes, and potential triggers. They can explain the importance of lifestyle modifications, such as avoiding sudden head movements or specific positions, to minimize symptoms. They can also provide information about exercises or vestibular rehabilitation programs that can help improve balance and reduce the impact of vertigo on daily activities.

It's important to note that the scope of a family doctor's involvement may vary depending on their expertise and available resources. Collaboration with specialists can ensure comprehensive care for patients with complex or persistent vertigo.

Vertigo in emergency department

In the context of acute symptoms of vertigo, this often means that the patient cannot get an appointment for examination in the outpatient clinic in a reasonable time. Therefore, although patients know that their lives are not in danger, many of them decide to seek help in the hospital emergency department (ED). On the one hand, treatment protocols in the emergency department are based on the exclusion of the most urgent clinical conditions, such as bleeding, infarction, acute infectious disease, or traumatic injury. Therefore, the usual protocol in the routine examination at ED includes laboratory tests and a CT brain scans in addition to taking the patient's history and neurological status. On the other hand, there are only 4 hospitals in Croatia with ENT physicians in ED, while neurologists are available 24/7 in all 30 Croatian hospitals. For this reason, almost all patients with symptoms of vertigo are referred to the neurological outpatient clinic[2].

Unfortunately, analysis of all visits to ED shows that only 8% of all examinations of patients with vertigo symptoms revealed vertigo due to central nervous system disorders, while the majority had BPPV, functional vertigo, or secondary vertigo due to inadequately controlled chronic diseases (mostly arterial hypertension).

From all this, we can see several public health problems, both for the patients themselves and for the examining physicians. Due to symptoms of vertigo, patients seek the most accessible doctor, in Croatia this is the doctor in the hospital ED[3]. In these patients, tests performed at ED show normal results in over 95% of cases. This fact further confuses patients, as their symptoms persist despite the normal findings. Furthermore, the protocols of ED are designed only to rule out the most urgent conditions, leaving no room for a more comprehensive approach to patients with vertigo. This is especially true for the patient's history, where the exclusion of trauma, disorders of consciousness, and febrile conditions are addressed in detail, while the description of vertigo symptomatology is usually very brief. In addition, due to the increasing workload on ED, physicians do not have the time to deal in detail with a patient who does not appear to be in a life-threatening condition.

The broader meaning of vertigo in the context of globalization and migrations

The term vertigo can also be more culturally determined, as many patients in Croatia use the term vertigo in a broader sense that includes both dizziness and unsteadiness, but also more diverse complaints of balance disorders. This is an example of

[2] Bilić, I., Vujčić, M. i Košta, V. (2022). Analiza rada hitnoga neurološkog prijma Kliničkoga bolničkog centra Split u jednogodišnjem razdoblju. Liječnički vjesnik, 144 (9-10), 319-322. https://doi.org/10.26800/LV-144-9-10-5

[3] Croatian Health Statistics Yearbook 2021, Croatian Institute of Public Health, 2022, Zagreb

just one society and a nation. Today's times, marked by many migrations, but also by the integration of different cultures into the domicile one, brings a different understanding of health and illness. Vertigo can be a symptom or a disease, but it can also be an indicator of a certain condition depending on its cultural affiliation. With the aim of providing the best possible treatment, the doctor who examines the patient must increasingly consider and respect the different understandings of the term vertigo. Vertigo, as a symptom, can occur in individuals across different cultures. However, the perception and interpretation of vertigo may vary depending on cultural beliefs, practices, and healthcare systems. Here are some cultural aspects that may influence the understanding and management of vertigo.

Traditional Medicine

In many cultures, traditional medicine systems exist alongside Western medicine. Traditional healing practices may have their own explanations and treatments for vertigo, often rooted in cultural beliefs and practices. These can include herbal remedies, acupuncture, Ayurvedic medicine, or traditional Indigenous healing methods.

Cultural Interpretations

Cultural interpretations of vertigo may vary. Some cultures may attribute vertigo to spiritual or supernatural causes, such as possession by spirits or imbalances in energy flow. Others may view it as a physiological condition, like a problem with the inner ear or a result of stress or anxiety.

Cultural Stigma and Perception

Cultural stigmas surrounding certain health conditions, including vertigo, can impact individuals' willingness to seek medical help or discuss their symptoms openly. Cultural beliefs and attitudes towards illness and disability may influence how individuals perceive and cope with vertigo.

It is important for healthcare providers to consider cultural factors when assessing and managing vertigo in patients from different cultural backgrounds. Understanding a patient's cultural context can help in providing culturally sensitive care, promoting effective communication, and respecting their beliefs and preferences in the management of vertigo.

Conclusion

In summary, a potential solution to this so-called "vertigo issue" may not require many changes in the healthcare system, but rather additional education of patients and healthcare providers. First, public campaigns should focus on educating patients that dizziness, as a very common symptom, is usually not life-threatening. Second, patients should be taught how to describe their symptoms to their physicians as accurately and clearly as possible. This would reduce the time needed to make the correct diagnosis and provide appropriate treatment. It would also save patients and the health care system unnecessary diagnostic procedures. Finally, primary care providers, especially primary care physicians, should be trained in the diagnosis and treatment of patients with vertigo through continuing medical education programmes. If this succeeds, it will result in better patient care, better understanding of vertigo, and earlier initiation of appropriate treatment, which in turn will result in fewer visits to hospital emergency rooms and reduce the financial burden on the health care system.

References

1. https://www.theguardian.com/society/2023/feb/08/nhs-waiting-lists-in-england-unlikely-to-fall-in-2023-research-suggests, accessed 20.02.2023.
2. Bilić, I., Vujčić, M. i Košta, V. (2022). Analiza rada hitnoga neurološkog prijma Kliničkoga bolničkog centra Split u jednogodišnjem razdoblju. Liječnički vjesnik, 144 (9-10), 319-322. https://doi.org/10.26800/LV-144-9-10-5
3. Croatian Health Statistics Yearbook 2021, Croatian Institute of Public Health, 2022, Zagreb

Diagnosing Functional Neurological Disorder in Croatia. What can be changed?

Slaven Lasić[1], Filip Đerke[1,2], Jasna Badžak[1], Petra Bago Rožanković[1,3]

[1] Department of Neurology, University Hospital Dubrava, Zagreb, Croatia
[2] Department of Psychiatry and Neurology, Faculty of Dental Medicine and Health, JJ Strossmayer University of Osijek, Osijek, Croatia
[3] School of Medicine, Catholic University of Croatia, Zagreb, Croatia

Dear Editor,

In this letter, we present our opinion, subserved to sociological data, on an underwhelming state of affairs concerning the public, and medical community opinion of functional neurological disorders in Croatia.

Functional neurological disorders abbreviated "FND" (ICD -10 F44, F45) are defined as various neurological symptoms such as limb weakness, unexplained sensory symptoms, cognitive disorders, gait difficulty, movement disorders, or paroxysmal episodes which are inconsistent and incompatible with current knowledge of known organic neurological diseases (1). The prevalence of FND is estimated to be 50 per 100 000 population per year with an incidence of 4 to 12 per 100 000 population per year (2). Total costs of ED visits and inpatient care of adult FND in the USA are above $1.2 billion annually (1) comparable to hardest-to-treat neurological diseases. Current understanding of FND has advanced with neurobiological data of altered neuronal networks, and the exclusion of necessary stressor agents advancing its understanding from previous definitions such as psychogenic, conversive, or medically unexplained neurological disorders. Combining detailed medical history, and clearly defined positive signs in neurological examination demonstrating inconsistency allows this to be a safe diagnosis with the frequency of misdiagnosis being 4%, and with a rate of reversal of diagnosis being only 0.4% (2). Neurologists› role is paramount in treating FND starting with an adequate explanation of diagnosis, arranging a multidisciplinary treatment plan (physiotherapy, cognitive behavioral therapy by psychologists, and non-pharmacological methods), and follow-up of patients. Early diagnosis, honest follow-up, and discourse show promising results in treating this disorder (3).

FND as a diagnosis in Croatia is still underrecognized by primary physicians, neurologists, patients, and the general public. No adequate scientific research on it is represented in the Croatian scientific bibliography search engine (CROSBY) with keywords such as "dissociative disorder" entered in search engine resulting in 28 papers, "conversive disorder" presenting 10 papers, "psychogenic" presenting 8 papers, and "functional neurological disorder" presenting 0 papers (4). FND is often mentioned to be second to headaches with regards to outpatient neurological visits, and the CROSBY keyword "headache" produces 276 results showing the disparity in coverage of these diagnoses in Croatia. According to the Croatian Public Health Department Mental disease Bilten (5) morbidity percentage

OPEN ACCESS

Correspondence:
Slaven Lasić
lasicslaven1993@gmail.com

This article was submitted to RAD CASA - Medical Sciences as the original article

Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Received: 31 March 2023
Accepted: 15 May 2023
Published: 26 June 2023

Citation:
Lasić S, Đerke F, Badžak J, Bago Rožanković P. Diagnosing Functional Neurological Disorder in Croatia. What can be changed? 556=62-63 (2023): 114-115
DOI: 10.21857/ypn4ocdr79

of mental diseases in primary health care is highest in diagnoses encompassing neurotic, stress-related, and somatoform diseases (F40-F48) with around 50% of mental disease patients in primary care being with those diagnoses. Hospitalization rates of F40-F48 are 9% among hospitalization rates of mental health diseases (5). Even though there is no isolated analysis of F44 and F45 diagnoses, and many of these patients are not adequately coded these percentages show that their number is significant. Unfortunately in Croatia public opinion and the opinion of physicians are still inadequately differentiating FND as a term from psychogenic, factitious, and even malingering meaning that it is often understood by the patient and physician as to be a stigmatizing diagnosis. Lack of up-to-date education of physicians leads to administering multiple tests which rise the expenditure of resources and leads to patients› suspicion of having a rare medically unexplained disease. This combined with an inadequate explanation of the disease leads to "doctor shopping" for years solidifying these symptoms, and making them harder to treat. Neurologists in Croatia unfortunately often dismiss these patients after diagnosing them, leaving them to be treated by psychiatrists, while other less self-confident neurologists fear missing a rare neurological disorder and failing to grasp the latest research results about FND.

Symptoms of these patients are involuntary, and as real as are of other organic neurological diseases. They should be recognized as such and provided specialized physiotherapy, cognitive behavioral therapy, TMS, and necessary medical aids in refractory cases. For a small country such as Croatia dedicated FND clinic with inpatient rehabilitation would be a possible solution for treating and destigmatizing these patients nationwide.

Sites like www.fndhope.org and www.neurosymptoms.org are recognized in English-speaking spheres as valuable assets in patient-physician communication. Using the same template in Croatian could potentially be rewarding alongside self help booklets. Any information helping patients understand their diagnosis results in better acceptance and better treatment response. Education of physicians about novel neurophysiological findings in FND should help them understand this disorder better giving more confidence in diagnosing it thus creating better opportunities in starting adequate treatment earlier. Introduction of annual seminars in continuous medical education, creation of national guidelines, algorithms, promotion of psychologists, and physiotherapists› role in multidisciplinary treatment are all ways that would guarantee advancement in the current state of FND treatment in Croatia.

References

1. Stephen CD, Fung V, Lungu IC, Espay AJ. Assessment of Emergency Department and Inpatient Use and Costs in Adult and Pediatric Functional Neurological Disorders. JAMA Neurol. 2021;78(1):88-101.
2. Espay AJ, Aybek S, Carson A, Edwards MJ, Goldstein LH, Hallet M et al. Current Concepts in Diagnosis and Treatment of Functional Neurological Disorders. JAMA Neurol. 2018;75(9):1132-1141. doi: 10.1001/jamaneurol.2018.1264.
3. Gilmour GS, Nielsen G, Teodoro T, Yogarajah M, Coebergh JA, Dilley MD et al. Management of functional neurological disorder. J Neurol. 2020;267(7):2164-2172. doi: 10.1007/s00415-020-09772-w.
4. CROSBY site https://www.bib.irb.hr/ accessed 20.02.2023.
5. Silobrčić Radić M, Švigir I. Veličina problema mentalnih poremećaja u Hrvatskoj. In Brkić Biloš I, Silobrčić Radić M eds. Mentalni poremećaji u Republici Hrvatskoj. Zagreb, Hrvatski Zavod za Javno Zdravstvo;2022: 2-26. pp. ISBN 978-953-8362-22-4

Book review:
The history of tuberculosis - with reference to sanitation and tuberculosis in Mraclin”

Author:
Željko Cvetnić

In the appropriate classicist space of the Revival Hall of the National House of the Croatian Academy of Sciences and Arts in Gornji Grad, on February 16, 2023, academician Željko Cvetnić's sixth author's title "The History of Tuberculosis - with reference to sanitation and tuberculosis in Mraclin" was presented, published by the Institute for Scientific Research and artistic work of the Croatian Academy of Sciences and Arts in Velika Gorica.

The book consists of an introduction, 8 large chapters with numerous sub-chapters, a conclusion and a glossary. It is a complex work that deals in a very systematic and detailed manner with a widespread and significant disease that has characterized the entire human history. Starting with the first information about tuberculosis in prehistoric times and ending with the final vision of a world without tuberculosis. Scientific and medical discoveries, treatment trends, as well as the most important events related to tuberculosis in the international framework, i.e. in research and achievements of the broad scientific community, are described. With a global view, the situation in Croatia is described, but also locally in the context of the disease and public health efforts to combat it. The

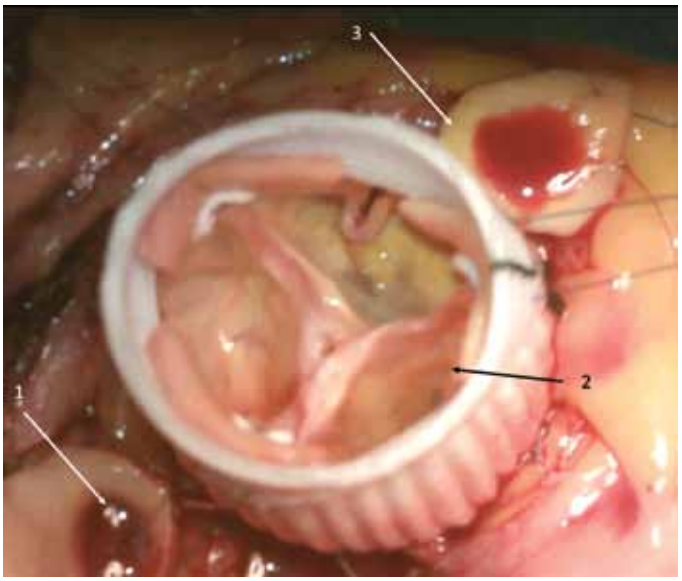
village of Mraclin in Turopolje is highlighted in two chapters, where the fight against tuberculosis took its extremely interesting course and which in some way became a model for the hygienic efforts of public health experts and the community in preventing and controlling the disease in the entire public health world. On the historical medical side, the chapters under the title: diagnosis, prevention and treatment of tuberculosis - from sanatoriums to antituberculosis drugs, in which a clear overview of the development of tuberculosis sanatoriums in general and especially in Croatia, surgical interventions in the treatment of tuberculosis, and the history of important diagnostic methods, development and application of tuberculin and Calmette-Guérin (BCG) vaccine. It is important to emphasize that this book collects in one place important data in a national framework about the traces that point to this disease in prehistory, antiquity and throughout the Middle Ages, the modern era up to the 20th century, as the most important tuberculosis epidemic throughout history. The book The History of Tuberculosis with reference to sanitation and tuberculosis in Mraclin is certainly one of the fundamental historical medical studies published in our country, which will serve as a relevant source for scientists working on this topic, but also for everyone who wants to know the history of this disease and the struggle to overcome it as and the current state of the disease and its projections for the future.

As emphasized at the beginning of the presentation by the presenters, Academician Dario Vretenar, Secretary General of HAZU, Academician Vida Demarin, Secretary of the Department of Medical Sciences of HAZU and Academician Zvonko Kusić, President of the HAZU Foundation, the interest in this presentation with eminent guests from Zagreb, Croatia and abroad was impressive. Reviewers - associate professor Ph.D. Željko Dugac, assistant professor Ph.D. Stipica Grgić and prim. Dr. Vera Katalinić Janković pointed out the author's balanced approach to the interdisciplinary nature of this scientific, social and cultural topic, they especially pointed out the way in which he managed to fit various aspects into a whole accessible not only to the profession but also to a wider audience. The basic message of the book is based precisely on the example of Mraclin, in which Dr. Andrija Štampar, in the 1920s and 1930s, set a historical roadmap towards a "world without tuberculosis".

Aortic valve reconstruction workshop

Authors:
Hrvoje Gašparović
Gebrine El Khoury

Historically, aortic valve replacement has been the gold standard for the management of aortic stenosis and insufficiency. While the former pathology still remains, almost exclusively, the subject to replacement, patients with aortic regurgitation are increasingly offered reconstruction of their valve. The only similar option for aortic stenosis is commissurotomy, which is a procedure reserved for the pediatric population. Its limited durability makes it inappropriate for adults. Conversely, aortic valve repair in the setting of aortic valve regurgitation has become increasingly more popular. Its appeal and superiority stem from the reduction of foreign material within the bloodstream with a subsequent reduction in infectious and thrombotic potentials, as well as the reduction of anticoagulation and its bleeding associated complications. Of importance is also the fact that it provides superior hemodynamics. Surgical techniques of aortic valve repair are complex and designed to address a specific morphologic feature of the regurgitant aortic valve. The procedure frequently involves remodeling or replacing the entire aortic root, whilst preserving the native valve. There are two major surgical options. These are the remodeling and the reimplantation techniques of valve sparing aortic root replacement. Regardless of the employed surgical technique, understanding the complex geometry of the aortic root is paramount. Bicuspid aortic valve morphology adds another layer of complexity to an already complex operation. This goal oriented workshop aimed to provide its participants with an opportunity to refine their skills and add new skills to their surgical armamentarium. Aortic valve reconstruction provides an important new avenue of management for patients with aortic regurgitation. Providing reproducible and durable results is crucial in wider dissemination of these techniques.



8th Croatian Symposium on Vascular Medicine - CROVASCULAR 2023

Authors:
Mislav Vrsalović [1,2]
Nikola Kos [2]

[1] University of Zagreb School of Medicine, Zagreb, Croatia
[2] Department of Cardiology, Sestre Milosrdnice University Hospital Centre, Zagreb, Croatia

On March 3, 2023, the annual Croatian Symposium on Vascular Medicine - CROVASCULAR 2023 was held for the eighth consecutive year in Zagreb, at the National Home Palace of the Croatian Academy of Sciences and Arts.

The symposium was organised by the Department of Medical Sciences of the Croatian Academy of Sciences and Arts, the Sestre Milosrdnice University Hospital Centre Zagreb and the Croatian Cardiac Society.

This symposium traditionally gathers numerous experts in the field of vascular medicine to popularize angiology and raise awareness about the prevention and treatment of vascular diseases. The motto of the meeting was "holistic approach to the vascular patient", and thus renowned cardiologists/vascular medicine specialists, interventional radiologists and vascular surgeons participated and contributed to interesting discussions after each session.

In his opening speech, the chairman of the Organising committee and head of the Department of Vascular Diseases and Arterial Hypertension at the Sestre Milosrdnice University Hospital Centre Zagreb, prof. Mislav Vrsalović, spoke. Prof. Mislav Vrsalović emphasised the importance of early detection and treatment of patients with polyvascular diseases, not only for improving the life quality of patients, but also for reducing cardiovascular morbidity and mortality. He stressed the importance of such meetings, where paradigms from current guidelines are eagerly discussed and included in everyday clinical practice. It is noteworthy that the first Croatian Prospective Peripheral Artery Disease Registry (CRO-PAD) was established at the Sestre Milosrdnice University Hospital Centre in 20101-8. The purpose of this single-centre prospective database was to assess risk factors, prognosticators, cardiovascular and limb events, as well as to develop therapies and improve patients' healthcare and disease outcomes.

Figure 1. Dr Bjorn Dario Franjić, prof. Vinko Vidjak, acad. Zvonko Kusić, acad. Vida Demarin, acad. Davor Miličić, prof. Diana Delić-Brkljačić, prof. Mislav Vrsalović, prof. Aleš Blinc, prof. Davor Vagić, prof. Miljenko Kovačević, prof. Ljiljana Banfić, prof. Goran Krstačić (from left to right) in the Revival Hall, National Home Palace of the Croatian Academy of Sciences and Arts (Zagreb) during 8th Croatian Symposium on Vascular Medicine - CROVASCULAR 2023.

Acad. Vida Demarin opened the meeting on behalf of the Croatian Academy of Sciences and Arts and expressed her satisfaction with the great interest in the Croatian Vascular Symposium and in vascular medicine in general. The president of the Croatian Cardiac Society, acad. Davor Miličić noted in his welcome speech that significant progress has been made in the detection and treatment of peripheral vascular diseases in recent years. Prof. Davor Vagić, director of the Sestre Milosrdnice University Hospital Centre, highlighted the hospital's long tradition in vascular medicine in his welcoming speech. He was also pleased that in 2022 the Sestre Milosrdnice University Hospital Centre was appointed as the Referral centre for peripheral and polyvascular artery disease of the Ministry of Health of the Republic of Croatia.

The symposium sessions covered almost the entire spectrum of vascular medicine: prevention, diagnosis and treatment of peripheral arterial diseases, new findings in the field of venous thromboembolism, interventional and surgical treatment of the aorta, peripheral arteries and veins. The lecturers and moderators were eminent cardiologists, angiologists, vascular surgeons and interventional radiologists, from medical schools in Zagreb, Split, Rijeka, Osijek and Ljubljana.

The state-of-the-art lecture was given by prof. Aleš Blinc from the University Clinical Centre in Ljubljana, entitled "Thalidomide use in refractory arteriovenous fistulas". One of the sessions was organized in collaboration with the Croatian Society for Vascular Surgery and included the topics on aortic diseases. In addition, data on the epidemiology of vascular diseases in Croatia was presented to the Croatian cardiovascular community for the first time.

The last session was dedicated to challenging clinical scenarios and diagnostic and therapeutic dilemmas in the field of peripheral arterial and venous diseases.

In conclusion, prof. Vrsalović summarised the the most important findings and invited all physicians interested in vascular medicine to participate in the 9th Croatian Symposium on Vascular Medicine - CROVASCULAR 2024.

References

1. Vrsalovic M, Vrsalovic Presecki A, Aboyans V. Cardiac troponins predict mortality and cardiovascular outcomes in patients with peripheral artery disease: A systematic review and meta-analysis of adjusted observational studies. Clin Cardiol. 2022;45(2):198-204.
2. Vrsalović M, Batinić T, Kos N. Gender differences in risk factors and cardiovascular outcomes in symptomatic peripheral artery disease patients. Rad Hrvatske akademije znanosti i umjetnosti. Medicinske znanosti. 2021;548(56-57):22-27.
3. Vrsalovic M, Aboyans V. Antithrombotic Therapy in Lower Extremity Artery Disease. Curr Vasc Pharmacol. 2020;18(3):215-222.
4. Vrsalović M, Presečki AV. Atrial fibrillation and risk of cardiovascular events and mortality in patients with symptomatic peripheral artery disease: A meta-analysis of prospective studies. Clin Cardiol 2017;40(12):1231-1235.
5. Vrsalovic M, Vucur K, Vrsalovic Presecki A, Fabijanic D, Milosevic M. Impact of diabetes on mortality in peripheral artery disease: a meta-analysis. Clin Cardiol 2017;40(5):287-291.
6. Vrsalović M, Vucur K, Jelakovic B. Atrial fibrillation predicts cardiovascular outcome in hypertensives with symptomatic peripheral artery disease and preserved ejection fraction. J Clin Hypertens (Greenwich) 2016;18(9):953-4.
7. Vrsalović M, Vučur K. Diabetes and critical limb ischemia: the deadly duo in patients with symptomatic peripheral artery disease. Acta Clin Croat 2016;55(2):240-245.
8. Vrsalović M, Vučur K, Car B, Krčmar T, Vrsalović Presečki A. C-reactive protein, renal function, and cardiovascular outcome in patients with symptomatic peripheral artery disease and preserved left ventricular systolic function. Croat Med J 2015;56(4):351-6.

Figure 2. Croatian Symposia on Vascular Medicine - CROVASCULAR 2015-2023.

Primary Sjogren's syndrome, multidisciplinary approach in diagnosis and treatment

Author:
Jadranka Morović-Vergles

The Scientific Symposium on "Primary Sjogren›s syndrome, multidisciplinary approach in diagnosis and treatment" was held in Zagreb, Croatia, on March 10th 2023 in the National Hall of Croatian Academy of Sciences and Arts, and was organized by Department of Medical Sciences of Croatian Academy of Sciences and Arts (HAZU), Academy of Medical Sciences of Croatia and Global Alliance for musculoskeletal health of Croatian Medical Association.

Organizers of the symposium were Prof. Jadranka Morović-Vergles, MD, PhD and Academician Vida Demarin.

Primary Sjogren›s syndrome (pSS), is a chronic and heterogeneous disorder characterized by a wide spectrum of glandular and extraglandular features. It is a systemic autoimmune disease with prevalence ranging from 0,03% to 5% in different countries. Most patients with pSS suffer from dry eyes, dry mouth and fatigue which leads to poor quality of life. In at least one-third of patients, there may be associated extraglandular manifestations (cutaneous, pulmonary, renal, peripheral and central nervous system, articular, muscular and hematological involvement), therefore a multidisciplinary approach in diagnosis and treatment is very important.

The meeting started with a welcome speech by the secretary of the Department of Medical Sciences of HAZU Academician Vida Demarin, who, as co-host of the symposium, opened the meeting by emphasizing the importance of multidisciplinary and team work in medicine.

The beginning of the symposium was marked by the opening lecture of Prof. Jadranka Morović-Vergles, MD, PhD from Dubrava University Hospital under the title "Primary Sjögren›s syndrome", which gave an overview of the etiology, epidemiology, diagnosis and clinical picture of pSS with special reference to the importance of multidisciplinary approach to both diagnosis and treatment of these patients.

Then Prof. Ivan Alajbeg, PhD from the Faculty of Dentistry of the University of Zagreb, in a lecture entitled "Oral cavity in primary Sjögren›s syndrome", spoke about the dry syndrome that often occurs in elderly, that can also be triggered by some medications, and highlighted the peculiarities and differences that characterize pSS. He also stated the indications for a biopsy of minor salivary glands, a minimally invasive procedure performed in the oral clinic at the Faculty of Dentistry.

After that, in the lecture "Aspects of pathological diagnosis of primary Sjögren›s syndrome», associate professor Lovorka Batelja, MD, PhD from the Faculty of Medicine of the University of Zagreb spoke in detail about the importance of pathological diagnosis and the data that the pathohistological analysis of salivary gland biopsies consistent with the diagnosis of pSS must contain.
Prim Melanie Ivana Čulo, MD, a rheumatologist from the University Clinic Vuk Vrhovac, in a lecture "Application of ultrasound in the diagnosis of primary Sjögren›s syndrome", spoke about the importance of an ultrasound examination of the salivary glands by a rheumatologist and further monitoring of the patient.
About the importance of laboratory parameters in the confirmation of diagnosis of pSS spoke Lovorka Đerek, PhD from Dubrava University Hospital in a lecture entitled "Laboratory diagnosis of primary Sjögren›s syndrome», and after that associate professor Ljubo Znaor, PhD from Faculty of Medicine of the University of Split detailed the diagnostic methods and treatment of the eye in pSS in a lecture entitled «The eye in primary Sjögren›s syndrome, diagnostic methods and treatment».
This was followed by a lecture by Academician Vida Demarin entitled "Neurological manifestations in primary Sjögren›s syndrome», in which the manifestations of the central and peripheral nervous system in pSS were presented in detail, along with the methods of treatment.
Professor emerita Dušanka Martinović Kaliterna from the Faculty of Medicine of the University of Split, introduced us to cardiac events in pSS as well as depression and fatigue in these patients in a lecture entitled «Fatigue, depression and cardiac events in primary Sjögren›s syndrome».

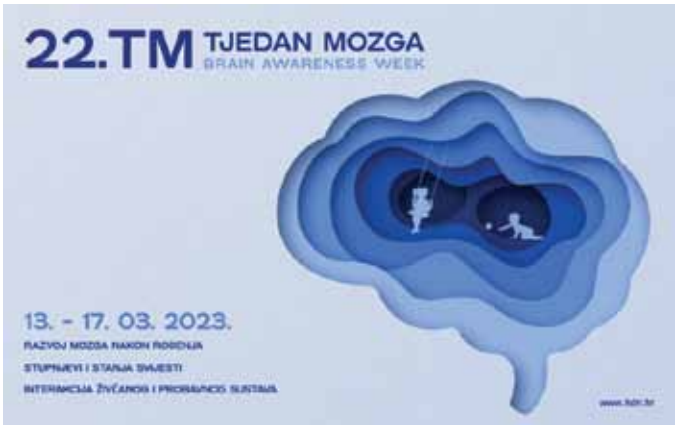
Academician Mirna Šitum presented in detail dermatological aspects of this syndrome and methods of treatment in the lecture entitled "Dermatological aspects of primary Sjögren›s syndrome».

In the second part of the symposium, after the break, Prof. Krešimir Galešić, MD, PhD from Dubrava University Hospital spoke about kidney involvement in pSS, which can sometimes be the first manifestation of this syndrome in a lecture entitled "Kidney involvement in primary Sjögren›s syndrome». Then Jasna Tekavec-Trkanjec, PhD from Dubrava University Hospital, spoke about the lung involvement and pulmonary manifestations in pSS in the lecture entitled "Lung involvement in primary Sjögren›s syndrome», and assistant professor Joško Mitrović, MD, PhD from Dubrava University Hospital, in the lecture entitled "Joint involvement and treatment of primary Sjögren›s syndrome», spoke about arthralgias/arthritis in pSS, and also about the treatment of SS in detail, which is primarily in the "hands" of a rheumatologist.
At the end of the symposium, Prof. Vlatko Pejša, MD, PhD from Dubrava University Hospital spoke about lymphomas and primary Sjogren›s syndrome in a lecture entitled «Primary Sjogren›s syndrome and lymphomas".
The symposium ended with a round table discussion in which all participants took part, and it was concluded that a multidisciplinary approach is extremely important, especially in the diagnosis of pSS. In addition to diagnostics, the good cooperation of various specialists in the treatment and follow-up of patients with pSS is no less important, which affects patients' better quality of life and outcome.
The meeting lasted for 6 hours and 30 minutes.

Brain Awareness Week 2023 - Symposium "Neurobiology, ontogenesis, and evolution of consciousness and self-consciousness in humans"

Authors:
Alisa Junaković
Janja Kopić

The 22nd Brain Awareness Week in Croatia organized by the Croatian Institute for Brain Research and Croatian Neuroscience Society was held from March 13th to 17th. The main topics this year were postnatal brain development, levels of consciousness, and brain-gut interaction. As part of Brain Awareness Week, a mini-symposium "Neurobiology, ontogenesis, and evolution of consciousness and self-consciousness in humans" was organized by the Department of Medical Sciences of the Croatian Academy of Sciences and Art, Croatian Neuroscience Society, Croatian Institute for Brain Research, Centre of Excellence - "Centre for basic, clinical and translational neuroscience", and International Institute for Brain Health. The exact biological basis of consciousness and especially self-consciousness has not been resolved, so many interesting lectures helped us understand this topic better. Several invited speakers from Croatia participated in the symposium - Academician Ivica Kostović (introductory lecture "Developmental neurobiology of the emergence of consciousness and self-consciousness in humans"); professor Miloš Judaš, president of the Croatian Neuroscience Society ("The evolution of consciousness in the light of Damasio's theory"); Professor Darko Chudy and Dr. Marina Raguž ("DBS in disorders of consciousness"); Professor Miro Jakovljević ("Self-awareness, self and empathy in normal and abnormal mind"); Professor Marko Radoš and Professor Milan Radoš ("Functional MRI as an indicator of brain areas involved in the biology of the self"). Professor Neven Henigsberg gave us a lecture on a popular topic: artificial intelligence ("What are the limits of the artificial?"). "Disorders of consciousness in daily practice" was a very interesting clinical lecture held by Dr. Hrvoje Budinčević and Academician Vida Demarin. Professor Ante Sekulić gave us a lecture on an intriguing topic named "Biological basis of general anesthesia" and the lecture "Consciousness and memory" was held by Professor Goran Šimić and Professor Mario Vukšić. All lectures gave us an insight into the complex and intriguing topic of the neurobiology of consciousness and self-consciousness but also left many open questions for further research.



News in Andrology Symposium

Author:
Zoran Zimak

The 1st "News in Andrology Symposium" began with opening remarks from Academician Vida Demarin, Secretary of the Department of Medical Sciences at the Croatian Academy of Sciences and Arts (HAZU), and Academician Željko Kaštelan, President of the Organizing Committee.

The first session was chaired by Željko Kaštelan, Igor Grubišić, and Antun Gršković.

Zoran Zimak discussed the techniques of Testicular Sperm Extraction (TESE) and microdissection TESE (mTESE) and provided insights into their appropriate applications in the context of male infertility treatment. He shared the results achieved at the University Hospital Center Zagreb. The excellent success rates of both procedures underscored the institution›s commitment to delivering high-quality care and aligning with global standards of excellence in the field. Mirsala Solak from the University Hospital Center Zagreb examined the use of hormonal stimulation as a potential approach in addressing male infertility, exploring its efficacy, controversies, and current status in clinical practice. Antun Gršković, an assistant professor at the Medical School of the University of Rijeka, highlighted considerations, and best practices for diagnosing and treating varicoceles, a common condition associated with male infertility, addressing optimal timing and techniques involved. Professor Lana Škrgatić focused on the preparatory measures and considerations for women undergoing assisted reproductive techniques, providing valuable insights into optimizing the success rates of these procedures.

The second session was moderated by Dinko Hauptman, Domagoj Rašić, Žana Saratlija, and Ivan Ćosić.

The session started with an interesting lecture about cardiac patients and erectile dysfunction. Ivo Planinc discussed the relationship between cardiovascular conditions and erectile dysfunction, shedding light on the impact of cardiac health on male sexual function and potential strategies for managing this connection. Professor Ida Šamanović explored the psychological aspects of erectile dysfunction, emphasizing the importance of providing comprehensive support and counseling to individuals facing this condition. Žana Saratlija delved into the topic of penile rehabilitation following radical prostatectomy, discussing various

approaches and interventions aimed at optimizing post-surgery outcomes. Igor Grubišić provided an overview of reconstructive surgical techniques employed in the management of penile conditions and abnormalities, highlighting advancements in this field. Ivan Ćosić focused on the treatment options and advancements in managing urethral strictures, a condition characterized by narrowing of the urethra, discussing surgical and non-surgical approaches. Dinko Hauptman addressed the topic of male incontinence, examining the various strategies and interventions available for managing this condition and improving the quality of life for affected individuals. He displayed the advancements achieved at the University Hospital Center Zagreb, highlighting state-of-the-art therapeutic procedures, including the implantation of artificial urinary sphincters and the implementation of sacral neuromodulation techniques. His presentation underscored the commitment to delivering cutting-edge care and innovative solutions in the field of male incontinence.

The event drew over 100 participants, including specialists, medical students, and researchers, fostering vibrant discussions, and emphasizing the need for a comprehensive and multidisciplinary approach to andrological care. In his final words, the President of the Organizing Committee, Academician Željko Kaštelan, concluded the event by highlighting the significance of a multidisciplinary approach in andrological patient care and expressing optimism for future successful symposiums, contributing to the further development of the field in Croatia.

4th Course in Clinical Psycho-Neuro-Endocrino-Immunology (PNEI)

Author:
Sanja Toljan

4th Course in Clinical Psycho-Neuro-Endocrino-Immunology (PNEI) was held from 10.-13.5.2023. in Zagreb. As usual, participants gathered from all parts of world to hear and learn from experts in novel approach to health and disease. Organized by HAZU and Poliklinika Orlando, the course is an example of scientifically grounded medicine, but applicable in everyday practice. Akademkinja Vida Demarin and dr Sanja Toljan, founders of the Course presented the history of PNEI, its meaning for modern medicine and the principles of PNEI (anatomy, physiology, function, integration). The emphasis was to give different approach to medicine as it has been taught nowadays, integrative versus separate. Although it is much easier to follow body systems in separation, in real life they are coordinated, driven mainly by central nervous system. Integration of brain, immunity, endocrine system and the body performance is complicated to follow, but modern science gave us many insights into it.

The course teaches the circadian rhythm alignment, neuroplasticity, microbiome function, inflammation, the principles of anti-inflammatory therapies like physical activity, diet, pharmacotherapy of low dose medicine. Special emphasis is on diagnostics in PNEI medicine, like testing the cortisol diurnal curve and estimating the allostatic load in each individual.

After the course, the participants comment as „their heads were full of new information “, it was above their expectations to hear so many new things, but with solid foundations in science.

The 5th Course in PNEI is planned for spring 2024.

Air pollution, noise, and arterial hypertension – global risk. Environmental hypertensiology 2

Author:
Ana Jelaković

On 11th and 12 th of May 2023, Croatian Hypertension League organized the second international symposium of environmental hypertensiology. This year the topic was air pollution, noise, and blood pressure- global risk. Like last year's hybrid symposium on climate changes, this hybrid meeting was also under the auspice of the Croatian Academy of Science and Arts. More than 250 participants learned and enjoyed in lectures given by leading experts in hypertensiology, cardiology, nephrology, diabetology, lipidology, endocrinology, pulmology, neurology, public health, epidemiology, paediatrics, kinesiologist, nutritious, but also meteorology and chemistry.

First session was reserved for chemists, biometeorologist, and climatologist to explain how they measure air pollution, what are the types of pollution particles and how does the network of air pollution stations across the country works. The topics then moved to epidemiology and colleagues from National Public Health Institute gave data on all-cause and cardiovascular morbidity and mortality related to the air pollution. From public health data and epidemiology, symposium continued from genetics and endothelial function, to hypertension, and extended on every aspect of cardiorenovascular continuum including early vascular aging. Particularly interest was a talk on air pollution and telomers given by leading world geriatrician Athanase Benetos from France. Before section on cardiovascular diseases, we heard what the link of air pollution and noise with obesity is, as well with metabolic syndrome, liver disease, diabetes, renal function, chronic kidney disease, and thyroid gland disease. It was interesting to learn how air pollution and noise affect diseased people on haemodialysis, and after kidney and heart transplantation. Second day started with neurology. Interesting talks were given on how air pollution and noise contribute to cognitive impairment, stroke, obstructive sleep apnoea and dementia. Air pollution and climate changes change pollen allergen season and impact severity and duration of asthmatic lung disease as well as chronic obstructive lung disease. It is easily assumed how air pollution and noise can contribute to lung cancer prevalence and outcomes. Last section was very interesting organized by a multidisciplinary team of experts comprised from nutritionist, kinesiologist, mental health specialist and public health experts. Air pollution and climate changes impact the quality of our food, disrupt physical activity benefits one can engage. Thus, a broader view on individual and public approach is urgently needed to grasp to this ongoing change and try to ameliorate further impact on human health. In total, 42 presentations were delivered, with a lot of brisk discussion after every section.

The symposium ended with round table were both public health experts met with clinicians and authority representative from Ministry of Economy and Sustainable Development. With this symposium which is continuation of the last years on climate changes, the Croatian Hypertension League and Croatian Academy of Science and Arts are showing their primacy and leadership in general wellbeing and health preservation. It is our hope that this would contribute to increasing awareness of general population, physicians, and other experts how we all are responsible. We wish that our government not only to continue with all activities already on the way, but to be even more active in decreasing effects of air pollution on the health of our nation. Beside individual effort and physicians' awareness of air pollution and noise impact on health, it is up to government officials to ensure better multidisciplinary teams of environmental specialist, urban planners, and biometeorologist who will plan our environment and sustainable living. Mitigation and adaptation to air pollution and climate changes, as well to noise, should be more developed without any delay.

The whole symposium is recorded, and all lectures and discussions are available at the educational web site of the Croatian Hypertension League and the Croatian Society for Hypertension, so all who would like to learn are welcome.

Meet the expert during the coffee breaks.

Controversies in Hypertension, Cardiovascular Prevention and Nephrology

This year's Controversies in hypertension, cardiovascular prevention and nephrology organized by Croatian Hypertension League and Croatian Hypertension Society were held a hybrid meeting on 12th and 13th May. The well accepted form of pre-recorded high-quality presentations and live on-site moderated discussion were very well attended with 250 on-site participants and 420 virtual attendees. First session started with life-style modification panel with multidisciplinary experts (neurologist, diabetologist, nutritionists, kinesiologist, psychologist). Round table broad one of many controversies: is for women longevity more important to lose weight or to be physically active? First day finished with panel discussion on treatment of metabolic aspects in hypertension (dyslipidaemias, hyperuricemia, diabetes). The second day started with panel discussion on always difficult to answer question in hypertensiology and nephrology like - how to treat supine hypertension, can antihypertensives aggravate or lead to depression, how to treat frail and elderly, or when to stop or avoid corticosteroids in glomerular disease. The highlight of the second day was brisk round table on harm reduction in smokers. Some controverse issues were mentioned, and raised lively discussion on whether smoking should be classified as a disease, and to be treated accordingly, how to prevent children to start smoking any nicotine product, how to avoid misleading premise that there are unharmful nicotine products etc. In every Controversies there is a section on hypertension in pregnancy and hypertension and metabolic disturbances in children and adolescents. These are vulnerable populations and knowledge on how to diagnose and treat hypertension is always lacking. Following was mixed panel discussion on themes from cardiology aspect of hypertension and emerging new subspeciality of hypertensiology: oncohypertensiology. Oncology treatment thanks to new and *smart* drugs is getting more and more successful, and oncology survivors now live longer and beyond their oncology path. Unfortunately, most of new oncology drugs affect heart and kidney, and have side effect- hypertension. It will take a subspecialist to understand and properly treat this growing high cardiovascular risk population. New Croatian consensus paper on renal denervation was launched. Whit this paper Croatia in a head of our European peers and ahead of forthcoming new European hypertension guidelines. The second day was rounded with panel discussion on supplement prescription, where nutritionist and pharmacists show how much their expertise and input are necessary in multidisciplinary team treating hypertensive patient. Nevertheless, every clinician must be knowing which supplement and OTC drug its patient is using, as well how to give proper advice on these products. Sections organized during the coffee breaks - Meet the expert- are venue where usually younger colleagues can speak to expert in certain field and to ask questions in more informal surrounding. Meet the expert coffee breaks are very popular. Controversies ended on Sunday morning with two round tables; one on COVID-19 vaccines side effects and second round table with controverse question in renal replacement therapy: home haemodialysis vs. peritoneal dialysis. All pre-recorded presentation are available on https:/e/hdh.emed.hr/kontroverze-2023 and are free for interested health care providers to broad their understanding of complex and diversly aspects of hypertension and associative disorders.

Lectures and panel discussion

MIND & BRAIN – 62nd International Neuropsychiatric Congress, Pula, Croatia - May 18th-21st, 2023

Authors:
Hrvoje Budinčević
Vida Demarin

The 62nd anniversary of our traditional Mind & Brain - International Neuropsychiatric Congress was held again in Pula from May 18th - 21st 2023.

The Congress was organized by International Institute for Brain Health and Department of Medical Sciences of Croatian Academy of Sciences and Arts, together with Society for Neuropsychiatry, Faculty of Dental Medicine and Health - J.J. Strossmayer University of Osijek, Croatian Society for Personology, Personality and Eating Disorders, Central and Eastern European Stroke Society (CEESS) and Croatian Stroke Society under endorsement of the World Federation for Neurology (WFN). The Congress was accredited by Croatian Medical Chamber and the Croatian Council of Physiotherapists.

Due to our traditionally excellent scientific program, bridging neurology and psychiatry and adjacent disciplines, there were 300 registered participants. Similar to previous years our program was interesting for participants outside from Central European countries, e.g. South Africa, Israel, United States of America, Ireland, Italy and Australia. In-person format gave us excellent opportunity for discussion in more human environment.

First day of the Congress was reserved for registration and networking activities. The Opening of the Congress involved special guests the mayor of Pula (Mr. Filip Zoricic) and the president of Istria Region (Mr. Boris Miletic) who opened the Congress. The scientific program on 19th and 20th May started with Plenary sessions.

During Plenary session Vida Demarin and Radwa Khalil presented inspiring lectures on arts influence on brain and possibilities of creative therapy on neuroplasticity and neurorehabilitation. Further plenary lectures on Friday were related to less common disorders such as restless legs syndrome, myasthenia gravis and the relationship between botulinum toxin and depression. Plenary session on Saturday was primary related to psychiatric themes and its relationship with neuroinflammation, and gut-brain interactions. The special lecture was intended as a memorial to the scientific research in schizophrenia of our honorary Kuratorium member prof. Gerd Huber. Academic lecture was given by Leontino Battistin on reflections of a clinician to the actual trends in clinical neurosciences.

After Plenary session the Congress was divided into two parallel sessions on following topics: Graz Stroke Symposium, Old-age psychiatry symposium, Neurodegenerative Symposium, Pula Multiple Sclerosis Symposium, Migraine Symposium, Sport's Psychiatry Symposium, Epilepsy Symposium, Medical Ethics Symposium, Free Topics Symposium. A Workshop on multidisciplinary approach to acute stroke was organized. The Psychopathology Summer School with focus on schizophrenia was led by prof. Karl Bechter, prof. Martin Brüne and prof. Dominique Endres. Poster session involved 41 poster presentation. Three best posters from neurology and three from psychiatry were awarded by prizes, the first two prizes given by the City of Graz, and second and third prizes were given by INPC Kuratorium and International Institute for Brain Health. Satellite Symposia were rich with recent data on the newest therapeutic possibilities and achievements. The last day was reserved for Kuratiorium, Central and Eastern European Stroke Society and International Institute for Brain Health meetings and closing ceremony.

Altogether after these four days our Mind & Brain congress was very successful with lots of interactions and vivid discussions. Em-

inent lecturers from many parts of the world shared their enormous knowledge and expertise with young colleagues, widening the perspectives and opening the new paths and the new directions, following the founding idea of this congress: Pula School of Sciences and Humanity.
Save the date for the next year!

33rd Summer Stroke School "Healthy lifestyle and prevention of stroke and other brain impairments"

- Dubrovnik, June, 5th- 9th 2023.

Authors:
Hrvoje Budinčević
Vida Demarin

Our traditional 33rd Summer Stroke School "Healthy Lifestyle and Prevention of Stroke and Other Brain Impairments" returned after COVID pancemic to the Inter-University Center in Dubrovnik.

The Summer Stroke School as a part of academic program of Inter-University Centre Dubrovnik, was organized by International Institute for Brain Health and Croatian Stroke Society, and co-organized by Department of Medical Sciences of the Croatian Academy of Sciences and Arts, Central and Eastern European Stroke Society It is accredited with 4 ECTS credits and by Croatian Medical Chamber and Croatian Council of Physiotherapists. Founder and Course Director is Vida Demarin, who successfully run the school together with Board Directors Roman Haberl, Kurt Niederkorn, and Hrvoje Budinčević.

The program of the school is traditionally inspiring and rich with recent knowledge, what was the reason that attracted participants from following countries: Croatia, Montenegro, Austria, Bosnia and Herzegovina, Germany, Israel, North Macedonia, Slovenia and Albania.

The opening by Vida Demarin included the introduction to 33rd Summer Stroke School and the lecture on psychoneuroendocrinoimmunology as a new paradigm shift to clinical work. Recent news and approach to migraine was presented. During first three days the cerebrovascular ultrasound hands-on workshops were organized. The most of topics covered important topcis regarding stroke, especially acute stroke treatment and stroke prevention. The themes were focus to: stroke risk factors (arterial hypertension, diabetes, air pollution, psychiatric disorders) and sex differences in stroke, stroke mimics, imaging in stroke, acute stroke treatment (thrombolysis and thrombectomy with use of drip-and-fly model and telestroke), issues regarding direct oral anticoagulants, transient ischemic attack, secondary stroke prevention with usage of dual antiplatelet therapy, management of carotid artery disease and intracranial arterial disease, stroke complication (spasticity), and imunosenescence and cerebrovascular diseases. Presentations on treatment of advanced Parkinsons disease and dystonia were reserved for the Friday.

A satellite symposium discussing the recent therapeutic possibilities in migraine and multiple sclerosis.

During this interesting program, participants were very satisfied with its content and opportunity to discuss in friendship atmosphere with lecturers and to have opportunity to try and practice ultrasound examination during Cerebrovascular Ultrasound hands-on workshop with individual approach.

See you next year in Dubrovnik from June 3rd to 7th, 2024.

Warsaw communiqué on climate change in Europe

Author:
Bojan Jelaković

Climate change is happening. It is affecting the entire planet from local to continental scale and in many spheres, notably the environment, society and economy. Humankind, especially in its activities related to energy and the environment, is caught in a difficult dilemma: it is both one of the main factors of climate change and one of the most vulnerable components of the system Earth. This dilemma is still far away from being solved, however, we already see that climate change means profound impacts and transformations, and that these differ regionally. Pursuant of the Anthropocene concept, the man-made climate change has a game-changer effect on the system Earth. By its magnitude and impact, climate change is most probably the global challenge of the century, not halting at state borders. This impact is already in the focus of many aims and measures, combining strategies of mitigation and adaptation. National governments, the European Union, the United Nations – all have put forward ambitious plans towards sustainability. However, there is no guarantee that such efforts will succeed. **The European Climate Conference (ECC)** was organized by the Polish Academy of Sciences PAN and Leopoldina Nationale (Deutsche) Akademie der Wissenschafhten, was held in Warsaw 15-16 May 2023. ECC had a clear focus on science. Leading experts from across the European continent shared latest insights on climate research and discussed related transformations through sectoral lenses. The ECC was venue where bridges between interdisciplinary research and society – assessing climate change in Europe were made, considering the continent's regional diversity and the resulting regionally differing approaches. It was my privilege to participate in this important conference on behalf of the Croatian Academy for Sciences and Art.

Conclusions of the conference were summarized in communiqué aiming to improve the public literacy on climate changes.

Warsaw Communiqué on Climate Change in Europe

The inaugural European Climate Conference has convened 90 scientists from 45 countries across Europe and Central Asia to assess climate change and the progress towards reaching climate neutrality. The assembled scientists hereby present the ensuing communiqué.

1. Climate change is happening, and planet Earth is in the age of the Anthropocene. Global warming and its consequences are caused by human activities, and this is one of the most pressing challenges of our time. Climate change impacts lives, businesses, settlements, and ecosystems. No individual and no planetary component remains unaffected.
2. The extreme manifestations of climate change include: heat waves, droughts, forest fires, heavy rain, floods, severe storms and cyclones. Additionally: changing seasonality, longer atmospheric pressure blocks, loss of glaciers and sea ice, sea level rise, ocean acidification and warming, and changes in ocean circulation. All these are highly likely to amplify by 2050.
3. The principal ecological manifestations are aggravated by climate change, but are primarily driven by deficient land, soil and water management. These include: loss of biodiversity, loss of ecosystem functions and services, soil degradation and desertification, and deterioration of freshwater resources.
4. The range of risks and the magnitude of transformations must be considered systemically and sequentially (phasing-in-phasing-out). Transformations need to be just, both within and among societies. The impetus for transformation is still not ambitious enough. We need to act faster and more comprehensively. Handling climate change requires harmonising mitigation and adaptation strategies, always in a cross-sectoral approach.

5. For energy and industry, the following measures are a priority: (a) accelerate the decarbonisation of energy production mainly through renewables, considering wide-scale electrification, cost and consumption efficiency, and negative emission solutions; (b) develop the Super Smart Grid (Europe, Central Asia, North Africa), combining engineering and market solutions to manage the variability of electricity from renewables with AI-based grid management; (c) invest in large-scale, long-term electricity storage (e.g. chemical storage through hydrogen); (d) support innovative approaches to de-fossilise industry and enable circular and low-carbon economy.
6. For biodiversity and ecosystems, the following measures are a priority: (a) significantly limit the causes of biodiversity loss and ecosystem degradation, especially deforestation, intensive agriculture (monocultures and overuse of pesticides) as well as overfishing, pollution, landscape fragmentation and land use conflicts; (b) opt for nature-based solutions to support climate mitigation and adaptation of species (e.g. by increasing genetic diversity); (c) implement the 2022 Kunming-Montreal Global Biodiversity Framework.
7. For agriculture and water, the following measures are a priority: (a) avoid soil degradation and carry out soil restoration; (b) integrate the management of land, soil and water, including water conservation, efficient irrigation and renaturation, and climate stress-resilient crops and livestock species; (c) limit resource-consuming agricultural production, especially for livestock (also to reduce methane emissions), and minimise food loss and food waste.
8. For infrastructure and mobility, the following measures are a priority: (a) follow new principles of integrated, resilient and responsive infrastructure planning, by connecting it to smart grids, resource-efficient mobility development, and low-carbon footprint building; (b) invest in electric mobility of people and freight, and simultaneously expand public transport; (c) consider climate risk management in business development and industrial policy, and in public administration and civil defence.
9. The regional diversity of climate (change) should receive more attention and be used as a strength in mitigation and adaptation actions. Local and regional knowledge should

be translated into national- and continental-level action for maximum effect. Using inherent potentials in Europe and the neighbouring Central Asia and North Africa, particularly for climate-neutral energy and food systems, should be prioritised and done in a fair, cooperative manner.

10. Policies and market-based instruments – especially game-changer, such as the European Green Deal, national green investment packages and national or supranational CO_2 pricing – should never work against each other. Climate and biodiversity policies should not be decoupled. Regulations should be used wisely to stimulate and scale technological and social innovations to achieve transformation. Research-based and transparent communication between politicians, citizens and scientists should become the norm to increase acceptance and reduce negativism and denialism. Generational equity and participative policymaking should be a matter of course.

Summary

The scientists participating in the inaugural European Climate Conference, representing 45 European countries, acknowledge that evidence-based scientific advice should be the basis for political and personal decisions for climate neutrality, and that scientists should engage more to increase climate change literacy of their fellow citizens. Effective actions for climate neutrality mean deep transformations of most aspects of the economy, the energy system, international markets, and the global cooperation framework. These measures should harmonise mitigation and adaptation strategies, and resolve transnational, national and regional trade-offs. Regional climate change and the global-local relationship should be more in the focus. Neither science, nor politics, nor collective civil action, nor education, nor public or private investments alone are enough. The window of opportunity for reaching the Paris Agreement goal is closing, and this leaves very few realistic options open.

The primary recommendation is to accelerate mitigation measures aligned with the Paris framework, while simultaneously deploying adaption measures. Regulation and financial instruments, such as CO_2 pricing, should be used to stimulate climate neutrality. This also includes incentives for openness toward green technologies, for rigorous reduction of greenhouse gas emissions, and for counteracting environmental pollution and ecosystem degradation, especially deforestation and biodiversity loss. Europe and Central Asia should make better use of their inherent potential to manage climate change: renewables, connectivity, market economy, people, knowledge, and innovations. Let us embrace these far-reaching potentials to accelerate the pace of transformation towards a climate-neutral future for our continent and for our planet.

ecc@europeanclimateconference.eu · www.europeanclimate-conference.eu

What is Elsa-Fluid? It is known. Eugen Viktor Feller – pharmacist and investor

Author:
Martin Kuhar

The Croatian Academy of Sciences and Arts recently commenced a cycle of lectures *Science in Focus*, whose purpose is to present in an accessible form the research conducted by its scientific research units, as well as its museums and galleries. As part of the aforementioned cycle, on May 17, 2023, Stella Fatović-Ferenčić (Division for the History of Medical Sciences) and Jasenka Ferber Bogdan (Cabinet for Architecture and Urbanism with the Archives of Fine Arts) held a lecture entitled *What is Elsa-Fluid? It is known. Eugen Viktor Feller – pharmacist and investor*.

The audience was welcomed by Marko Pećina, the Head of the Croatian Museum of Medicine and Pharmacy, who presented the lecturers and their most important contributions to their respective fields. He also greeted the members of the Academy (General Secretary Dario Vretenar, Ivan Gušić, Stjepan Gamulin and Mislav Ježić), members of the Feller family – great granddaughter Marta and great grandson Nikola Zdenković – as well as everyone in attendance. Pećina emphasized the interdisciplinary nature of the presented research, which was the result of a particularly fruitful collaboration between the Academy's two prominent research units. Finally, he informed the audience that the lecturers will alternate throughout the presentation.

The lecture started with the beginnings of the manufacturing process in Donja Stubica, which also represent the beginnings of the pharmaceutical industry in Croatia. The protagonist of the story was a Ukrainian pharmacist Eugen Viktor Feller (1871–1936), who came to Croatia from Lviv at the end of the nineteenth century and built a factory in Stubica for the production of the pharmaceutical specialty named Elsa-Fluid. The factory transformed Donja Stubica into a rather powerful transportation and financial hub which positively affected the economy of the region, while Elsa-Fluid made Feller a pioneer of pharmaceutical industry in Croatia. In the next several decades, his pharmaceutical specialties successfully broke into international market due to a carefully planned communication with consumers and a well-thought-out marketing strategy.

As a successful and wealthy entrepreneur Feller invested into real estate in Zagreb, where he relocated from Donja Stubica in 1904. There, he became known for his architectural production, thus contributing to the development of Croatian architecture. All the buildings he invested in were constructed and designed according to the contemporary stylistic norms, such as historicism, secession and Jugendstil, which speaks volumes not only about Feller's financial might, but also his sense for zeitgeist. House Feller on the King Tomislav Square, Europe House in Jurišićeva Street and Villa Feller in Jurjevska Street all contributed to the formation of modern Zagreb. It is no wonder, then, that this pharmacist was also a promoter of art, architecture, design, painting and sculpture at the beginning of the twentieth century.

In 2021, the lecturers published a book entitled *What is Elsa-Fluid? It is known. Eugen Viktor Feller – pharmacist and investor*, which was the result of a decades-long research about a topic previously only covered in folk legends. At the end of the lecture the book was given to the interested members of the audience free of charge.

Ninth Days of Andrija Štampar: Štampar's Ideology and its Opponents – Yesterday, Today, Tomorrowr

Author:
Martin Kuhar

From its inception in 2004 and under the auspices of the Croatian Academy of Sciences and Arts, the Days of Andrija Štampar in Slavonski Brod became a recognizable brand and a platform for discussions on wide-ranging medico-historical topics, especially those directly concerning Andrija Štampar, the pioneer of public health and one of the founders of the World Health Organization, as well as contemporary issues in the organization of healthcare. Five years after the last conference, finally on 31 March and 1 April 2023, the Ninth Days of Andrija Štampar were held at the Hotel Art in Slavonski Brod. The break caused by the coronavirus pandemic not only offered a space to reevaluate Štampar's fight against acute infectious diseases in the first half of the twentieth century, but also provided precious time for a more objective gaze on various measures undertaken in the global attempt to defeat Covid-19. Taking all these factors into consideration, the scientific committee decided to dedicate the Ninth Days of Andrija Štampar to the analysis of Štampar's ideology and its opponents in the past, present and the future.

The conference, which was organized by the Croatian Medical Association and the General Hospital "Dr. Josip Benčević", was welcomed by the following members of the organizing committee: Mario Blekić, MD, PhD, the President of the Croatian Medical Association – Subsidiary Slavonski Brod, Josip Samardžić, MD, PhD, the director of the General Hospital "Dr. Josip Benčević", Mirko Duspara, MD, the Mayor of Slavonski Brod, and Danijel Marušić, DVM, the Prefect of Brodsko-posavska County. After the ceremonial opening, Martin Kuhar, MD, PhD and Professor Ivica Balen, MD, PhD, promoted the book *Andrija* Štampar authored by Ivica Balen and Marica Jandrić Balen. The book was published in 2019 as part of the edition Croatian Giants by the publishing house Privlačica from Vinkovci. With extensive use of Štampar's own reflections on various events and topics, it chronologically follows the life of Andrija Štampar and thus represents another respectable contribution to what is now a substantial amount of work that came out of the Days of Andrija Štampar.

During the two-day conference twenty researchers in a very interdisciplinary composition presented their valuable research. General historians, historians of medicine, physicians, economists, museologists, art historians, ethnologists and cultural anthropologists, pharmacists and the historians of pharmacy – they all reinforced the potency of Štampar's ideology. Its longevity was discernable not only in its original domain – public health, which until very recently operated under extreme duress and substantial pressures – but also at the level of basic research, which underscored the importance of primary prevention of disease.

Almost traditionally, the Croatian Academy of Sciences and Arts participated at the conference with three speakers: Prof. Silvija Brkić Midžić, the Manager of the Croatian Museum of Medicine and Pharmacy, Prof. Stella Fatović-Ferenčić, MD, PhD, the Director of the Institute for the History and Philosophy of Science, and Martin Kuhar, MD, PhD, research associate at the Division for the History of Medical Sciences. Silvija Brkić Midžić presented a part of rich photographic collection kept at the Museum that best reflects Štampar's ideology. Martin Kuhar and Stella Fatović-Ferenčić presented the results of their research on the photographic material contained in Božidar Špišić's work on the rehabilitation of war veterans during the First World War, which was recently published in a prestigious journal *International Orthopaedics*. Together with Ivan Lukovnjak, Stella Fatović-Ferenčić brought a contemporary angle to Štampar's views through an innovative form of presentation – an "interview" with Štampar.

There are not many people in Croatia's scientific past that still can, many decades after death, gather researchers from multiple fields of study. Štampar's intriguing life, replete with seemingly insurmountable obstacles and challenges, still attracts modern interpreters who find in him not only an inspiration, but also solutions for myriad challenges plaguing modern healthcare.

DOI: 10.21857/yq32ohxg69

ESSAY - INTERVIEWS

MOST ILLUSTRIOUS ALUMNI OF THE SCHOOL OF MEDICINE, UNIVERSITY OF ZAGREB, ZAGREB, CROATIA

Dear Readers,

In the issue 544=52-53 of our periodical, RAD HAZU – Medical Sciences, we introduced a new feature entitled *ESSAY – INTERVIEWS „Corresponding Members of Croatian Academy of Sciences and Arts, Department of Medical Sciences* ". For the issues 54-55,56-57,58-59,60-61 and the present issues 62-63 of our journal we decided to expand the scope of that series and include interviews with other internationally known alumni of the School of Medicine, University of Zagreb, Zagreb, so that we could profile even those alumni who are not Corresponding Members of the Croatian Academy of Sciences and Arts. This change of venue required us to change also the title of this series of interviews, and rename it in Latin **Illustrissimi alumni Facultatis Medicae Zagrabiensis.** The same interviews, translated into Croatian will be published on the electronic web site of the Medical Faculty **mef.hr**.

Dr. Ivan Damjanov, Emeritus Professor of Pathology, The University of Kansas School of Medicine, Kansas City, USA, who is also a Corresponding Member of the Croatian Academy of Sciences and Arts agreed to continue conducting these interviews. Like the initial interviews those in the present volume are produced under the same Latin title in cooperation with the editors of "mef.hr", the official website of the School of Medicine, University of Zagreb. The preface to the initial series of interviews is reprinted here for historical reasons and to show that the main goals and intentions for this series remain the same despite the changes of the title of the series. In the issues 58-59 there is one exception because Ivan Damjanov-Interview was conducted by Marko Pećina.

Marko Pećina

==========

The preface in the Issue 544=52-53

The present series was conceived as a set of informally recorded conversations with the best-known and internationally recognized graduates of the School of Medicine, University of Zagreb. The English version of these interviews is now being published by HAZU to make them accessible to a wider readership, including all those who do not understand or read Croatian.

The primary goal of this series of dialogues in RAD HAZU is to present and recognize the outstanding alumni of the School of Medicine University of Zagreb, Zagreb,Croatia. We hope that our readers will enjoy reading about the memorable events in the lives of these physician-scientists, their achievements, and scientific contributions that made them famous worldwide.

The emphasis of these discourses will be on the human side of science and medicine. Our goal was to give the interviewees a chance to reminisce about their trials and tribulations as well the happiness and fun they experienced in their lives. In other words, the objective of the interviews is and will be to give our esteemed interlocutors an opportunity to tell their life story in their own words and show us "how they did it" while still keeping their personal and professional lives in balance.

Finally, it's a good time to remind you, our readers, of the Latin saying "*verba volant scripta manent*", which justifies publishing so many written words that otherwise would have been forgotten. By producing these pieces, our purpose was to preserve the informal records of the lives and work of featured physician-scientists; and by transforming their verbal testimonials into written documents, leave a permanent trace of their activities for future generations in the archives of HAZU.

Marko Pećina
Ivan Damjanov

Nenad Bogdanović Interview

Nenad Bogdanovic MD, PhD
Professor in Geriatric Medicine
Karolinska Institutet
Department for Neurobiology, Caring Science and Society - NVS
Division of Clinical Geriatrics
NEO,
and
Senior Consultant
Geriatric and Neurogeriatric
Theme Inflammation and Aging
ME Aging R94
Department for Cognitive Disorders
M52
Karolinska University Hospital

e –mail: nenad.bogdanovic@ki.se

1. How did you decide to study medicine?

This is a very good question which is difficult to answer by simple saying that was a natural way or family heritage. Neither my mother nor my father were in the medical profession. My granduncle was a well-known doctor in Šibenik, known for his work on improving the health in our town during the first half of 20th century. He was a big joker and I admired him while I was a little boy. I liked to visit him and play with various instruments especially with the old x-rays machine he had hidden in the small room at the end of the corridor of his house. My granduncle died of a malignancy induced by x-rays since body protection at that time was very weak.

My interest in biology I can trace to my high school years and my biology courses I took in the 2nd Zagreb Gymnasium. I liked biology in general but my hobby was hunting and dissecting frogs and engaging in similar pastimes. Culminating my biology related activities was a treatise about the development of cardiovascular systems in vertebrates that I wrote by the time of my graduation. It was a demanding task since nobody around me could help me write it and there was nobody with whom I could discuss those topics. I was reading some biology books recommended by my teacher but nobody taught me how to write a scientific paper or an essay, how important it is to quote the literature appropriately and how to prepare a list of references at the end of the paper. I wanted to impress my teacher and did not include any references into my writing, thus trying to show off how well I know this scientific issue. Thinking about all this today I feel a bit ashamed about my ignorance and naivete. Nevertheless it was obviously an experience that I will never forget. I even asked my sister, who is an academic painter, to make a few drawings for me. These were definitely better than my text.

During my high school years my best friend (he is my wedding witness) got me interested in car engines. Building and dismantling motors became a consuming passion of mine. My favourite entertainment was removing the engine from Citroen 2CV that I could take out from the car in about 3 hours. That were the days. During the summer vacation I liked observing, studying the action and dealing with the motors of small fishing boats. TOMOS 4 was the very first outboard motor that fascinated me, followed by Seagull, VOLVO Penta and Fariman. I used to ride motorboats at sea even if the weather conditions were not optimal. Not once I did encounter very bad weather conditions at the sea but luckily without serious consequences. Weather conditions perplexed me ever since and even today I pay attention to the changes of the weather and follow carefully the weather forecasts.

During that period of my life I was also preoccupied intensely with basketball. In 1968 Yugoslavia was the basketball world champion and that was an impetus for us teenagers to start playing the game for good. Together with a gang of friends I joined Medveščak, a team that was in second division. I liked that since it was a really a combination of sport and social gathering. Our sport and social events taught me how to share good and bad with my close friends. It was a lesson for the rest of my life.

From what I have said so far, you can see that by the end of high school there were three things that were important for my future life: biology/anatomy, motors and weather. I had to decide what to study and choose between Medicine, Physics or Engineering. What should I be, I had to decide. A doctor, an engineer or a meteorologist? The simplest answer was to try to enrol in all three faculties at the same time. Since I had passed the entrance examination for all three faculties, I decided to try do study course at the same time in parallel and make the final decision of what to become for later on. Thus in September 1972 I first started attending the physics lecture and then one month later entered into the medical school. The pivotal moment were the first anatomy lectures, and the feelings that overwhelmed me upon entering the anatomy museum and having the first look at the complexity of the human body. From that moment I was sure that I want to spend my life studying the structure

and function of the human body. The anatomy course was so intensive that I did not want to continue with physics and even did not attend any lectures at the Faculty of Engineering. I was very sure that my future lies in medicine without actually knowing what future will bring to me. I continue with sport but to a lesser extent. Gradually I stopped playing basketball and started with tennis since the Medical School owned several tennis playgrounds in the vicinity of the main campus.

Did I have any ideals, conviction or beliefs by that time? Probably not fully formed but I definitely wanted to follow in the steps of my parents. They were my idols and I wanted to find a balance between their characters, on one side may father and on the other my mother. My father was a Supreme Court judge in Zagreb with a PhD degree in jurisdiction and a huge knowledge of jurisprudence knowledge acquired before WWII. His ideals were to devote his life fighting for justice, freedom from the influence of authorities, with an emphasis on strong personal identity and endless work for the right causes and legal duties. My mother was a caring and very social person, an ardent educator, tolerant to the maximum in all respects, ready in any time to share everything with everybody. That was a way how our family was functioning as an ideal unit. Both of them were helping everybody and never ever accepted any reward for that. The anecdote but absurd situation was when somebody left a bag (I don't know what was in that bag) in front of our door. My father came outraged and has sent my mother find that person and force him to take the "present" back.

Following the example of my parents I refused to be part of any group, political or religious or any other, or to yield to the pressure of such groups. Like my parents I have been trying to be progressive, to have empathy towards others irrespective of their background or origin. I was always impressed by those whose actions were based on knowledge and honesty, and had inherent personal values. That was and still is my *modus vivendi.*

Figure 1. 40 years of generation, Zagreb, The Croatian Medical Association, 1976

2. Did you enjoy your student days in Zagreb?

I did enjoy greatly those days. I met a bunch of new friends with some of whom I still have close contacts even though we live in different parts of the world. Those friendships are very important to me and I consider them to be among the most valuable "gifts" my Medical School gave me for life.
During my medical school years I was very active in student groups, including the student club called Koma. That was the place where we used to meet and share our problems as well as to take action at the faculty assembly to improve our student condition. Those days students were not considered to be partners or important factors in shaping our own educational process. The entire faculty was structured as a pyramid defined by hierarchy headed by the dean, a cadre of powerful chairmen and a wide base composed of the aching faculty. The students were practically not included in that power structure and our student's budget was negligibly small in that time.
One of the main goals of our student organization was to produce teaching material in form of transcripts of lectures for those subjects where our professors were was not able or not willing to write a textbook, or translate a text from a foreign language. The typical example was pathophysiology where we did not have any official literature but rather machine written short texts that was provided after we have heard each lecture. We were working day and night to get enough copies for the entire class using two Gestetners mimeographs which used to be always out of function after a few hours of printing. The copy machines were the accessible in the main administration offices but could not be used by us students.
The second important activity was improvement of teaching and education via a student teaching committee led by us and Dr. Branko Richter, the Professor of parasitology. His contribution to our studies during the first 3-4 years was immeasurable.

Figure 2. With NIKON microscope, I did have the most advanced one, 2001

I became involved in scientific work already at the second year when I joined the neuroanatomy group of Professor Kostović, which later expanded into the Croatian Institute for Brain Research. Thus I learned the basic principles of science and how to start thinking like a scientist. With that initial experience I was able to form a students' scientific committee that tried to attract students to enter science. We also organized small local scientific conferences and annual conferences for medical and dental faculties in the region. At the time, I became the student representative on the Scientific-teaching Council of our Medical School, where we accomplished what was considered to be impossible up to then. Thus in 1981 during the inauguration and of the leadership bodies of the Medical School, I led the student group requesting the right for students to nominate their own candidate for the position of educational vice dean. In response to that unexpected and unsettling situation for the new dean, the leadership of student organization has been replaced by the novices chosen by the faculty as trustworthy, and the entire "rebelian" student organization has been placed under the full «control» of the faculty administration. As an example our year budget was same as a cupboard that new student leaders got after the replacement.

3. What were your favourite subjects and which professors you still remember?

My favourite subject was anatomy and especially neuroanatomy that was taught by professor Kostović. He was my idol and became my scientific mentor after I had completed my medical studies. The second subject was clinical neurology. Dr. Stevo Knežević, the professor of neurology played a pivotal role in attracting me to clinical neurosciences. I was determined to pursue a professional and scientific career due to the combination of neuroanatomy and neurology I had studied under the guidance of these two professors.

4. As a student did you do some research or had some serious extracurricular interests?

After my examination of neuroanatomy I joined the Kostović lab. He just arrived from USA and continued working on human brain development which he began in America. Thus I became part of a very propulsive and world-renowned research group involved in the study of foetal brain development. It was a time when I was hard working trying to finish my student obligations on one side and scientific tasks formulated by Dr. Kostović on the other. I spent enormous periods of time drawing the neurons by camera lucida system, and endlessly examining the microscopic sections of the brain. I tried to get the 3D image of dynamic foetal brain in time and space and that was extremely demanding but the results of my efforts from those days I am seeing even today. I still remember fondly that my first scientific question was how to understand the development of *induseum griseum*.

Figure 3. 2004 with Nobel laureate in medicine Richard Axel Columbia NY

Figure 4. Professor Bengt Winblad

5. While you were studying in 1980s there were not too many neuroscientist in Zagreb, or am I wrong? How did you decide to enter neuroscience not knowing exactly what you would like to study?

At that time Ivica Kostovic was the leading neuroscientist in the field of neuroanatomy especially developmental brain anatomy. After his arrival from USA and his historic description of the subplate layer the neuroanatomy in Zagreb had got the enormous push and I was lucky to join the group at the very beginning. Kostović did have a strong connection with well known Croatian neuroscientists abroad who had provided an important scientific support like Paško Rakić, Krešimir Krnjević and Ante Padjen. It seemed that the neuroscience in Croatia has a good future. The scientific results published over the last few decades prove that the optimistic prediction was actually correct.

6. You entered science through neuroanatomy, and your first papers dealt with morphology of the foetal brain. Do you think that this was a good way to begin your future studies of the brain and its diseases?

I think that the most of my papers dealt with morphology, starting with several works on human development followed by animal models of cholinergic depletion to the clinic-morphological work on neurodegenerative disorders. Was that the good way I don't know but that was a way that I extremely liked and had shaped my position today, I do think successfully

7. Did you have any role models? Or in other words, did you have a clear idea what it meant to be a neuroscientist?

I did not have an idea what does it mean to be neuroscientist. I found that work with the brain was so cool and interesting. When this passion continued I gradually became a full fledged neuroscientist. Even as a clinician today I am neuroscientist since I am thinking as a basic and clinical researcher while I am meeting patients. Probably that I did have several role models, starting with Ivica Kostović and Stevo Knežević, followed by Bengt Winblad who was my mentor in the world of neurodegeneration here at Karolinska Institute in Sweden.

8. Did you dream of becoming a basic scientist, a future clinician or you always intended to combine science with clinics?

I do think that I always wanted to combine both basic and clinical work. Even after 10 years in basic neuroscience, being student demonstrator and assistant professor in anatomy and neuroanatomy, I felt that I needed to apply my knowledge in a clinical setting and in direct contact with patients. This way I feel that I am applying my knowledge of neuroanatomy and basic neuroscience to everyday clinical praxis of neurology.

9. Did your plans change after you moved to Sweden?

Sweden gave me the possibility to utilize my knowledge as a neuroscientist and neurologist in the entire new field of neurodegeneration that I could not find in that time in Zagreb. I am very much aware that my plans had expanded in non-presidential manner that I could not even dream 33 years ago

10. Was the move to Sweden one of those crucial events that changed your worldview for ever?

Definitely that is true. The circumstance that led to my move to Sweden was almost anecdotal. I was completing my neurology training for the New University Hospital that Zagreb which was supposed to become the modern state-of-the-art hospital and it was then under construction. I felt that I want to put into practice in that hospital my to great loves at that time, neuroanatomy and neurology. I wished to have some kind of conference or meeting that leading basic and clinical neuro researchers put their brains together. I was too young without so many connection in the world and I decided purposely to convince my clinical mentor Knežević and basic science mentor Kostović to organise a conference and invite the leading people in the field to come to Zagreb. I had tried to be the executive organiser and to do my best to get my dream realized. That was a very demanding task. When I did present my idea to Knežević he rejected it and the same happened when I presented this idea to Kostović. The reason why they did not like the idea I could not understand. Reflecting about those events today I think that they did not want to combine different fields where they are not confident and this type of combined field in the field of neurodevelopment and neurodegeneration was not common in the scientific society at that time.

Figure 5. Brain Net Europe meeting in Budapest 2005

I found myself in very uncomfortable situation, but I said to myself to try to use the trick which did work on the end of the day. I had approached to Kostović and said that Knežević is very interested in the conference and that we have a unique opportunity for brainstorming between scientists in these two areas of neuroscience. The same arguments I presented to Knežević, and finally they both agreed and the conference took place in Dubrovnik 1990. I was so happy that I decided to do my best to have the conference succeed.

Those days there were no companies organising scientific conferences so we had to do everything ourselves. Kostović had invited the leading developmental neuroscientists (Rakić, Mishkin, Braak, etc) and Knežević invited the leading authorities on neurodegenerative diseases, such as Winblad, Reisberg, DeLeon and several others. The conference was a great success, the book of the proceeding was published, and memories of the event lingered for many years thereafter in the minds of many participants. 30 years after conference took place, I meet many of them and most still remembered fondly the meeting in Dubrovnik. That meeting was part of my destiny, since there in Dubrovnik I met my future mentor Professor Winblad, I met his at the airport and drove him to the hotel. During that ride we discussed many topics of common interest. I consider it as the beginning of a long-lasting friendship. At the end of the meeting he invited me to Sweden. He was, namely, developing a new research and clinical centre and thus he suggested that I could be of a big help to him in his effort with my a basic science and clinical experience. At the same time he told me that I could master new research elements of clinical and preclinical treatment of neurodegenerative diseases, which would then help me establish my own neurology-neuroscience practice in Zagreb in the New Hospital. That was our original plan and rest is history.

11. How difficult was it for you to leave Zagreb and move to Sweden?

Theoretically it was not. After I received the invitation, my entire family moved to Sweden with the idea to stay there for 1-2 years. We were very enthusiastic by thinking how the new department in the new hospital in Zagreb would be opened soon. But the situation had changed after one year. Hospital was stopped to build, and 200 doctors got fired without any plan to be employed somewhere else in the health system. Those were very difficult times, since I and my wife lost our jobs and were practically in the street with our first child. But Sweden wanted us to stay and offered me to continue my (our) work. That was difficult but at

Figure 6. With Prof Knezevic a clinical mentor 2005

Figure 7. Krnjevic, Rakic, Kostovic, giants of Croatian neuroscience, Zadar 2005

Figure 8. At my clinical department 2006

that moment it was a survival move. The major difficulties were to leave my parents and my sister, Zagreb as a my town, friends and colleagues, almost my entire life behind. I was not worried about work in Sweden, I already had a project and scientific tasks but the environment all around us was totally new for me and my family

12. To a young Croatian physician contemplating a move to Sweden what advice would you give on how to survive the first few months or years in that Scandinavian country?

Very simple advice if they are aiming to work. Important is to come with extra knowledge and skills at hand and a clear idea what you want to accomplish. Scandinavian countries are very focused and practically oriented and are able to recognize if they are getting extra value for their money. They are willing to help with everything from the beginning regarding even the needs for rest of the family and children. The quicker you are in the system, the more valuable you are for the host. When I had arrived, I did have a working permit from the first day, kindergarten and flat fixed for the family, and all that helped of course.

13. What were your major professional challenges in Stockholm?

Entering into a new research and medical system was not so difficult, but it was quite challenging to master the local language and to understand the work and legal differences. The knowledge that you bring from your own country is an asset but how to apply it might not be so simple. Adjusting to the new work conditions and local routine should be grasped as quickly as possible. The daily work in the clinical setting in Sweden may differ considerably from the work one did in Croatia, but one must adjust. In the clinical setting there is a big difference than in Croatia. Relation between workers and leaders is extremely professional and respectful. I knew all my rights from the very beginning. I do think that is a common professional behaviour at least here in Sweden.

14. Did you join a group or did your start working with a senior scientist?

After arriving to Karolinska Institute I had joined the group where senior scientist was my mentor, but the group also included 3 additional scientists of my rank and 2 technicians

15. How long did it take you to establish your own research lab and form a research group?

Since arrived as a young scientist I had to enter a PhD program after one year. During that time, I could not establish the group but completing my PhD program I was given the opportunity to form my own neuromorphology lab and brain bank. A technician and a PhD student were also assigned to me to help me with my research. In parallel I did start working at the clinic but keeping my 50% preclinical research position.

16. Was there a critical moment when you realized that you „finally made it“ in Stockholm?

A critical moment of that kind occurred during the first year of my stay in Sweden. It was not an earth-shaking event but I still

remember my outburst of joy and happiness after I successfully completed an immunostaining for demonstrating the enzyme cholintransferase in tissue sections. I was working on neurosurgical stereological lesions of nucleus Meynert performed to deplete the cholinergic innervation of the brain. That was an animal model for pharmacological treatment of cognitive impairment, which a very popular topic at that time. I got this task due to my skills in neuroanatomy and morphology as well as I learned psychological testing of experimental animals. One of procedures that I still had to master was immunostaining. The technician in the group where I had started was considered to be an expert and was responsible for the immunostaining. She could not get staining done after endless number of trials and it was considered to be impossible to perform. Then I suggested some modifications of the staining protocol, based on my previous experience in Zagreb. I knew that this enzyme is very sensitive and the proper fixation and tissue preparation is crucial for immunostaining. I decided to do everything by myself hoping that I will get a result. It was a very stressful moment but I was highly motivated to succeed. At the end I managed to complete the immunostaining. I was so overwhelmed with emotions that I started to cry in my small room, but then I pulled myself together, and then came out and showed the results to the rest of my group. I knew that I am going to change my position in the group and from a visitor become a respectful and fully accepted member. After that I did have much more freedom especially after the missteps in the immunostaining protocol had been changed. That technician responsible for the immunostaining was later included in my own group and today we are best professional colleagues. For me this event showed how important it is bring knowledge and useful working skills from your native country, especially if you have skills that the host may not have.

Figure 9. In front of Karolinska Hospital 2006

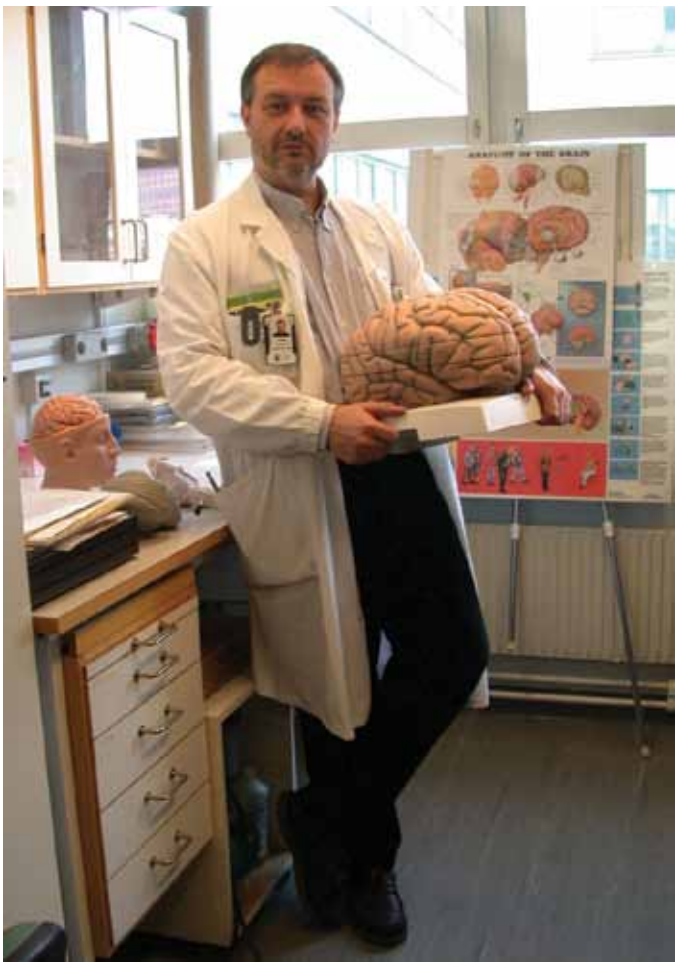


Figure 10. Clinician in the lab 2006

17. By nature are you a patient easy-going person or an impatient one who wants to have thing happen all at once, or as soon as possible?

Definitely not an easy going person. As a clinician and a senior physician I must be disciplined, plan ahead of time and stick to established protocols. I cannot improvise and I cannot postpone any assessment or plans for the patient care since so many persons are affected by my decisions. I try to resolve any issue during my working hours, and if possible never leave anything for later. The same applies to my preclinical research. But as any other human being I do make subjective estimates for some future events and actions, hoping that these problems could be resolved in near future. Accordingly, I am trying not to be a robot and remain flexible.

18. In a previous interview of yours that you gave to the Croatian magazine NACIONAL there is mention of a scientific award nick-named „little Nobel". When did you receive it, what for and what did it mean to you?

Ah that is a construct of the Croatian journalist. In 2004 I have been awarded by the highest pedagogic prize at the Karolinska Institute called Master of education. Students in Stockholm use to give this prize for their teachers who have excelled at education. I did get it for my teaching of neurology based on a combined clinical neurology neuroanatomy approach. To this end I would make a presentation of the clinical findings and then provide neuroanatomy material to supplement the clinical data. Students liked this multifaceted approach in which we juxtaposed clinical neurology with the dissection of the brain and neuropathology, combining morphology, functional anatomy and clinical symptoms. In real life situations the students were discussing clinical symptomatology by pointing out the anatomical regions on the fixed brains in the autopsy room. That was a pretty new and innovative approach at the Karolinska Institute and the students appreciated my efforts to integrate several aspects of neurosciences. Since the presentation of the student award coincides with the Nobel prize award, and since the Nobel laureate in medicine is present at the student festivities (I have a photo with him) the student prize was nicknamed "Little Nobel". The Swedish correspondent for Croatian news agency HINA did send short notice about it to Zagreb, but I do not know all the details about it. The prize that I received from students is mostly given to teachers involved in graduate education. I like teaching and thus I teach postgraduate courses in geriatric medicine, PhD courses in neurodegeneration, different courses for psychologist, nurses and courses for the Swedish medical doctors in training who are resident in neurology, geriatric, general and internal medicine. Moreover I do some lecturing for Croatian medical doctors regarding geriatric medicine.

19. From your curriculum vitae it seems that you have numerous functions and titles. I simply could not believe that a single person can do all that at the same time. Could you tell us how do you juggle all these responsibilities, assignments and tasks?

Ha ha ha I don't know which parallel functions you referring to, but it is true that I hold several active posts which are coordinated one with another, and thus quite manageable. Nevertheless, I work 12 hrs per day and most often I am on top of it, and finish on time my daily duties. For details about my private life you can ask my wife and she will tell you a few stories about her "absentee husband".

20. Which one of your papers do you consider to be your most important contribution to science?

I like to list three papers:
1. Volume and number of neurons of the human hippocampal formation in normal aging and Alzheimer's disease. G Šimić, I Kostović, B Winblad, N Bogdanović. Journal of Comparative Neurology 379 (4), 482-494, 1997
2. Bogdanovic N, Corder B, Lannfelt L, Winblad B. APOE polymorphism and clinical duration determine regional neuropathology in Swedish APP 670/671 mutation carriers: implication for the late onset Alzheimers's disease. J Cell Mol Med, 6(2):199-214, 2002
3. Environmental enrichment and the brain AH Mohammed, SW Zhu, S Darmopil, J Hjerling-Leffler, P Ernfors, Winblad B, Diamond MC, Eriksson PS and Bogdanovic N. Progress in Brain Research 138, 109-133, 2002
The first paper deals with the total number of neurons in the hippocampus. It is one of the only two papers in the world literature dealing with this problem. The method that was applied called stereology and we used it to estimate the total number of neurons in the structure. This paper was cited 609 times and is my most citated paper despite the field is very narrow.
The second paper deals with the clinics and neuropathology findings in the brains of patients who had the Swedish mutation. It is the first publication in the world dealing with this disease and discusses the gene-gene interaction in the clinical context.
The third paper as a big review deals with an environmental influences and plasticity of the morphology of the brain and we have stressed there the possible unique features of the Einstein brain

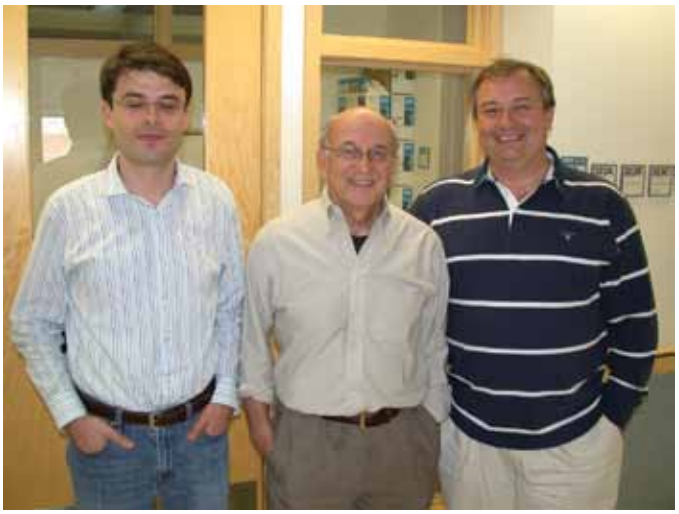


Figure 11. With Rakic and Sestan at Yale 2011

Figure 12. Explaining the brain to the patient, 2016 Oslo

Figure 13. Getting 1 mil dollars from mr Thon in Oslo 2017

21. Some of your papers are experimental, and some are clinical. Furthermore you are the discoverer of two Alzheimer disease mutations, Swedish and Arctic; I do not know how one would classify the papers dealing with such data. The question for you is as follows: How do you balance laboratory research and clinical investigations and all other activities that are hard to classify?

A shift in my research from classical preclinical experimental models to the clinical-pathological approach occurred a few years ago. As I have mentioned before, I was working 50% of my time as a clinician and 50% running the morphology lab and brain bank, which was collecting brains. In parallel with my clinical position I was also a consultant neuropathologist for 15 hrs per months assessing the the pathologic changes in post-mortem brains. The Swedish Ministry of Health has recognised my expertise in the field and awarded me this very unique position to analyse the postmortem brains from clinical cases that passed through my clinic. I was able to see all correct or mistaken diagnoses. In Sweden I did around 964 neuropathological autopsies with entire procedure of taking out the brain, preparing the tissue blocks for formalin fixation and frozen material. I was reading the slides and report the diagnoses, as very few neuroscientists do today. However, I feel that I should follow in the steps of the great neurologists/neuropathologists of previous times, including Alzheimer, Nissl, Fisher, Pick and several others. Concerning Swedish and Arctic mutations, I met those families as member of our team but I also did the first autopsies of patients with those unique mutations. Both mutations had led to the development of common mice models of AD. The work on the Arctic mutation 20 years ago enabled us to get the foundation for developing the first successful antibody against Alzheimer that were registered by FDA in January 2023 that got the name Lecanemab (Brand Name in the U.S.: LEQEMBI™)

22. You are best known internationally for your work on Alzheimer disease, and many of your publications deal with this topic. Maybe you could summarize in a few sentences your contributions to the genetics, clinical aspects and cell pathology of Alzheimer disease.

Most of my papers deal with the questions regarding Alzheimer neurodegeneration but I did also work on frontotemporal dementias, Lewy-body dementias, vascular and other neurologic diseases. To understand Alzheimer disease, we have to understand how it differs from other dementias. As I said previously understanding the genetics and unique morphological features of those two mutations that we discovered helped us to better understand presentation of the hallmarks of Alzheimer, amyloid plaques and tangles. The Arctic mutation has shown that pathology never reached the most advanced form of plaques but produces most toxic forms of protofibrils that are in focus

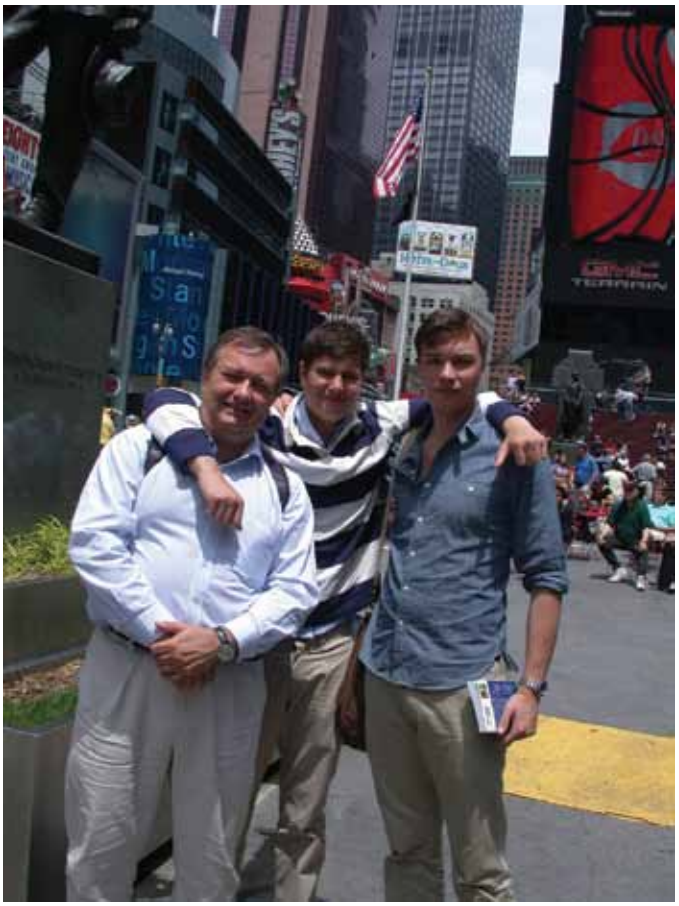


Figure 14. With my sons in Big Apple where I had a company HQ 2011

of antibodies currently registered this January by FDA. APOE lipoprotein, is coded by a gene that is one of the greatest risk genes for the Alzheimer disease in the elderly. In our Nature paper (*Nature Medicine,* 4:1182-4, 1998) we have stressed how APOE is involved in other diseases like HIV, as a contributing factor for cognitive impairment. My work on Swedish mutation and APOE has shown that gene to gene interaction can shape the clinical and morphological features even in mutation brains as mentioned earlier. Some of pioneer work I did on cholesterol function in the Alzheimer disease brain where astrocytes seem to be mostly involved (Neurosci Lett. 13;314(1-2):45-48, 2001). Other pioneering work was done showing the difference in intraneuronal amyloid concentration among the Alzheimer brain neurons regardless of mutation or idiopathic cause of the disease (Neuroreport. 2008, Jul 16;19(11):1085). At the clinical side of my research, I was always interested with the unusual clinical features and possibilities to test those differences, thus non-classical clinical presentation of the Fronto temporal Lobe dementias (Neuropathology. 2011 Jun;31(3):271-9, AJNR Am J Neuroradiol. 2009;30(6):1233-9), speech disorders and its testing (Cortex. 2007;43(5):60715, Folia Phoniatr Logop. 2009;61(5):269-274, Brain and Language, 79(2):333-339,2001, Logopedics Phoniatrics Vocology 2008 10:1-10)
Generally speaking, I have tried to be provocative in my work, trying to broad the field and challenging the established views. Was I successful or not I am not able to judge now.
Beside my clinical work I did some international education in the field of clinical development and organisation of the neurodegeneration department. The latest example was my engagement in Clinical Hospital Luohu in Shenzhen China where I spent some time during the 2018 and 2019 just before Corona pandemic. I did educate colleagues how to approach clinically to neurodegenerative diseases and what is the most important for diff diagnostic – I did established my small policlinic work and had some dozen patient that I did follow up.

23. You are actively working with drug companies on developing new drugs for the treatment of Alzheimer disease. How far did you get to reaching that goal?

I was actively working with 2 companies Wyeth and Pfizer on developing the anti-amyloid antibodies. It was 11 years ago when entire development of AD drugs failed due to several unfortunate factors. One of the specifically important reasons for this failure was that the clinical diagnosis of AD was established only on the clinical criteria. This means that doctors relied solely on identifying symptoms and signs of Alzheimer's disease without confirming the physical changes in the brain that typically accompany the disease. This approach resulted in misdiagnosis of patients, as other conditions with similar symptoms might have been mistaken for AD. Diagnosis of AD without the use of biomarkers or imaging techniques is no longer considered sufficient, as it can lead to incorrect diagnosis and inappropriate treatment. In USA use of biomarkers was not common and thus 30 % of wrong diagnosed patients were entered in the clinical trials in Phase 3. The results were disastrous for this field of drug development. We in Europe were using biomarkers for AD but we did not have a chance to continue the work since the drug company Pfizer had decided to terminate the program. Consecutively FDA had changed the rules how to perform clinical trials for AD. Overall, the changes in clinical trial rules and approaches to diagnosing AD have improved the accuracy and effectiveness of treatments for this devastating disease. However, there is still much work to be done to better understand the underlying biology of AD and develop more effective therapies for patients.

24. You have three patents to you name. Did these patents produce any tangible results so far?

Those 3 patents are as follows:
1) Apparatus for determining the volume of solid body and it's in real-time measurement, 2009. It has been in use while we

Figure 15. With my wife at the summer holidays 2015

Figure 16. In the depth of glacier at Spitsbergen islands

were working for 10 years on the project BrainNet Europe on the standardization of neuropathological protocols sponsored by Europe Committee. The main purpose was to standardise the method of measuring the shrinkage of the tissue. I personally did not have any financial benefit from this patent.

2) Method for purifying amyloid plaques, 2005.
3) Disease marker for AD and its use. 2003. This patent was related to the purification of the amyloid protein in the brain and its use as a biomarker. Both patents are part of the 10 years research collaborative project between Karolinska Institute and the Japanese company Sumitomo which is the ultimate owner of the patent.

25. You are interacting with scientists from other Scandinavian countries and are part of two European consortia for the study of the brain. Did some of your papers result from collaborative studies with scientist from other countries?

- BrainNet Europe is the project of EU granted for the period of 10 years to 20 different brain banks. Scientists, clinicians and neuropathologists in these banks worked together for many almost 10 years and have published more than dozen articles related to the standardization and harmonisation of the protocols related to utilisation of the brain tissue and characterisation of the pathological proteins.
- EUGMS is the European geriatric medicine Society the coordinated body for the all countries that have geriatric medicine as a specialisation. I am a member of the executive board and project COST (European Cooperation in Science and Technology) that is a funding organisation for research and innovation networks. That specifically aims to introduce the geriatric medicine specialisation in the south-east European countries. Croatia is a part of the project and I represent both Sweden and Croatia in attempt to build up geriatric medical services in my homeland. I am a specialist in geriatric medicine and have been licensed in Croatia as a first geriatrician. I am member of the geriatric working group of Ministry of Health in Croatia as an expert regarding establishing of geriatric medicine.

26. Perusing the list of you publications I see some names indicating that some of your collaborators are from our region here. Do you have any active projects with neuroscientists from the old country?

I am a visiting professor at the Medical faculty in Zagreb. I tach a postgraduate course at the Croatian Institute for Brain Research and I am an external mentor for PhD candidates at the Institute working on the ischemic perinatal brain lesions in animal models. I have an additional active collaboration with some scientist from the Institute more related to the specific experiments and articles that were published jointly. I am also involved in an active project on blood biomarkers for Parkinson and Alzheimer disease that is going on in collaboration with the neurology department at the University Hospital Rijeka.

Figure 17. At neurology clinic in China Shenzhen 2019

Figure 18. Patient in China 2019

27. Which projects preoccupy you currently the most and what are your short term and long term plans?

At Karolinska Institute and Karolinska University Hospital I am working on a project related to the characterization of amyloid fibrillar forms in the blood. We are using a sophisticated fluorescence techniques trying to develop it as a technique for the detection of future biomarkers. For that project me and my collaborators were highly awarded by Thon foundation from Norway and from diverse Swedish scientific and governmental foundations bodies (see photos)
The second project aims to improve the accuracy of dementia diagnoses in very old people who do not have amyloid proteins in their brain, but were previously misdiagnosed with Alzheimer's disease. The study will involve a comprehensive clinical assessment of individuals with suspected dementia, including cognitive testing, imaging studies, and other diagnostic assessments.
The researchers will use the latest diagnostic criteria for all types of dementia and will focus on identifying features that distinguish between different types of dementia, including Alzheimer's, vascular, frontotemporal, and Lewy body dementia. They will also examine the clinical course of the disease, including the progression of symptoms, response to treatment, and impact on quality of life. This project has significant implications for patient care, as accurate diagnosis is critical for appropriate treatment and care planning for individuals with dementia.
The third project: I am planning and excited to return to Boston University and continue important work, on von Economo neurons in monkey brains that I started many years ago with Prof Helen Barbas but due to my endless duties in Sweden the project was laying at the bottom of my desk. Specifically, these von Economo neurons have been implicated in the social and emotional processing of information, and studying them in monkeys can shed light on their functional significance in the human brain.

28. Do you have any plans for some collaborative projects with Croatian scientists?

I am keeping the long project with Rijeka, and COST program via EUGMS where the main aim is to establish geriatric medicine in the region using all possible country specific educational and professional contacts.

29. Any message for our younger colleagues considering to follow in your footsteps and move abroad?

My advice is to master certain techniques and skills while you are still in Croatia. Also try to establish contacts with colleagues from other parts of the world by publishing in international journals, attending congresses, making poster presentations, using different EU programs for student exchange, define you research interest together with mentor, get a PhD or post-doc position in Croatia or abroad. If you go abroad try to come back to Croatia and build up scientific infrastructure and initiate the national and international projects helping country to enter international family of scientist and putting Croatia higher at the scientific map. That privilege to be accepted back in the country of origin is the most valuable step in forming the new scientific environment and usually it is highly appreciated. I deeply regret that I did not get an offer and chance to come back earlier and share my experience with experts in Croatia.

Figure 19. With Queen Silvia at the grant award ceremony 2023.

Zoran Gatalica Interview

Zoran Gatalica, MD, PhD

Adjunct Professor of Pathology
The University of Oklahoma College of Medicine
Oklahoma City, OK

Advisory Board Member
European Society for Translational Medicine

e-mail:gatalicaz@gmail.com

1. Where did you grow up?

I was born in Bjelovar, a small town 80 kilometres east of Zagreb. Families from both my mother's and father's side lived in that region for centuries.

2. What do you remember from your high school days?

Those were happy times, and I still have very fond memories of my childhood. Carefree life in a small town had its own benefits and furthermore our town had a fantastic handball team. Our team, RK Partizan, Bjelovar had at that time won the handball championship of Yugoslavia several times, played several times in the finals of the European team championship and was even the European champion in 1972. That meant that RK Partizan was the champion of the entire world, since handball was played mainly in Europe. We youngsters were all very proud of our team and our town, and by inference we all felt quite important. The downside was that all the beautiful girls in our town were enamoured of handball players and other sportsmen; since I did not belong to that crowd, I was out of luck.

3. How did you decide to study medicine?

I made my final decision to try to enter Medical School in Zagreb during my senior year in high school, but I wasn't quite sure if that was something for me or not. I considered psychology and maybe even some other science career or engineering. At the end of the Medical School entrance exam, I wasn't even sure if I made it. I studied for the exam that summer of 1979, but there were "distractions", as any 18-year-old should have had. Eventually, and to my surprise, I was accepted. I got the news about this acceptance from my cousin while playing tennis, and still remember how I lost focus and thus the entire match against my best friend. I still regret it, even though, and for the record he was and still is a good tennis player.

4. How enjoyable were your first three preclinical years? What do you remember from those days?

I studied hard. I did well in some subjects and not so well in others, but overall, it was enjoyable. I met a beautiful girl who later became my beautiful wife. During the third year, I became a student preceptor ("demonstrator") in physiology and enjoyed quite a bit the opportunity to show off in front of my younger colleagues, while helping them learn the elements of physiology. Later on, I became a student preceptor in pathology, but it never occurred to me that I would ultimately choose pathology for my career.

5. Were the clinical years more enjoyable or more traumatic than the first three years?

I felt that I was well prepared for the clinical part of my medical school education and was eager to test what I learned in pre-clinical years. Accordingly, I enjoyed interacting with patients and instructors. It was gratifying to recognize symptoms of certain diseases in real life, and thus use the knowledge I acquired from books. For me, those years were never traumatic, and at some point I started enjoying the "easiness" of clinical years, maybe even a bit too much for my own good.

6. Which were your favorite subjects and favorite professors in the clinics?

My favorite clinical teacher must have been Dr. Danilo Tepavčević. He had a truly encyclopaedic knowledge, but he was also quite a character. He taught us everything with incredible enthusiasm and

Figure 1. Picture with my wife, Biljana, taken on the day of her graduation from the Medical School, in front of the old entrance to the Dean's office (Stari Dekanat)

love, even when we were not able to respond to his questions as quickly as he expected it from us. He suffered from Buerger's disease and by the time I met him he was already a double amputee. That handicap, however, did not prevent him from enjoying life (he was a great opera fan) and giving his students the best education possible (and occasional flick on the wrist).

7. Were you involved in any extracurricular activities during your student years?

As mentioned before, I have worked in two departments as a preceptor to make some money. At today's exchange rate it was not much, maybe, a couple of euros per session, but for a penniless student even that was a welcome relief.
I was active also in the Foreign Medical Student Exchange program. Our organization hosted every summer several medical students from all over the world, and we spent time with them and showed them around Zagreb and Croatia. During the summer after my fourth year it was my turn to go abroad and I spent a month in the department of internal medicine of the Royal Hallamshire Hospital in Sheffield. There, for the first time I was exposed to a clinical trial. It was exciting even though I do not remember much about the details of that study. I believe it was about prostaglandins and platelets in peripheral vascular disease. I also started a couple of research projects in the Department of Physiology under the mentorship of Drs. Nikša Pokrajac and Hrvoje Banfić. One of these projects, dealing with compensatory kidney growth led to my graduation thesis ("diplomski rad"). At some point I became very skillful in operating (nephrectomizing) mice; the skill had not left me and many years later I tried to revisit the idea during my time at UTMB, applying expression array analysis to detect growth mechanisms in uni-nephrectomized mice. Did not produce any meaningful result, mostly because the methodology (mice gene expression arrays) was still in its infancy.

8. What did you do after graduation?

After the internship, I became an instructor ("asistent") in Physiology. My daily tasks included teaching medical students and working in the laboratory on my doctoral thesis. Under the mentorship of Hrvoje Banfic, we worked on the effects of epidermal growth factor on the metabolism of the phospholipids, focusing on transmembrane signaling. It was a "hot topic" and I almost, literally once burned down the lab (I forgot to switch off some open flame, it caught fire) but luckily Hrvoje caught it in time and extinguished it.

9. Why did you join Dr. Banfić in the Department of Physiology ?

As a medical student I have spent many hours working in Dr. Banfic's lab and thus it was obvious to me that he would be an ideal mentor for my doctoral thesis. At that time he had recently com-

pleted his scientific doctorate and was willing to accept me and serve as my mentor. Furthermore, he had additional training at Cambridge, UK studying second messengers under Dr. Robin Irvine, one of the most influential researchers in that field at the time.

10. What did you learn from those few years spent in the Department of Physiology?

It felt like I spent much more time than the 3 years interrupted by a year of military service. Those were very important years in my postgraduate education. Among other things, I learned to design experiments and adopt assays, and to be always critical in evaluating the results before submitting them for publication. I also learned to write and evaluate scientific papers. In January of 1989, I defended my doctoral thesis entitled "The effect of epidermal growth factor on the metabolism of phospholipids in the rat renal cortical slices". Major results were published in 1988 (Gatalica Z and Banfic H. Epidermal growth factor stimulates the incorporation of phosphate into phosphatidic acid and phosphoinositides but does not affect phosphoinositide breakdown by phospholipase C in renal cortical slices. Biochimica and Biophysica Acta 1988 Mar 11;968(3):379-84).

11. Why did you move to the United States?

During my doctoral studies about the role of epidermal growth factor receptor, I interacted with Dr. Boris Mildner, who has a few years earlier studied EGFR in Philadelphia at the Wistar Institute with Dr. Barbara Knowles. Reading a paper that Boris wrote while working in the USA I saw that one of his co-authors was a certain professor at Thomas Jefferson University (TJU) in Philadelphia, by name of Ivan Damjanov, you probably know him (ha-ha!). I wrote to him and he accepted me to his lab in Philadelphia. The rest is history, that we are now recording.
My first travel across the Atlantic to Philadelphia was exciting and memorable. It coincided with the period during which the airplane company PanAm was going out of business. Thus, I missed several flights and finally arrived in Philadelphia, well behind the schedule and after midnight. Your wife Andrea and Hrvoje Vrčić, who already worked in your laboratory, picked me up in the middle of the night and took me to an apartment in Philadelphia on 13th and and Locust St. I was to share it with Hrvoje for some time. It was a cheap one but provided a lot of free entertainment. Suffice to say that the part of Philadelphia where we lived was at that time known as the "entertainment district". Several of our male and female neighbors living in the same apartment house were sex-workers.

Figure 2ab. Thomas Jefferson University, Philadelphia. I started as a postdoc in 1990 and later completed my residency training in pathology in 1996.

12. How did you decide to become a pathologist?

I worked as a student preceptor in anatomic pathology in Zagreb, but did not find it too interesting. It was mostly autopsy material (too late to impact patient's life). Later on, I attended some intraoperative pathology consultations as a 5th year student at Rebro University Hospital.It was interesting, but again my heart was then in physiology and biochemistry. I thought that microscopy was a bit too subjective. After learning that in America I can specialize in both anatomic and clinical pathology, and thus practice some clinical biochemistry, cytogenetics and even molecular genetics, it clicked with me.

13. After you finished your residency training in anatomic and clinical pathologist and passed your Board examination, you worked in Galveston, Texas and thereafter in Omaha, Nebraska. How valuable were those years in academic medicine?

During the residence training I had a privilege to learn from the best pathologists including Drs. Markku Miettinen, Bong Hyun, Peter McCue and Robert Peterson, to name a few. They taught me not just diagnostic skills, but more importantly, to conduct appropriate studies and utilize various methods of investigations on tissue samples. Thus, after turning down an offer from our Chairman Dr. Emanuel Rubin to stay at TJU, and following the suggestion of Dr. Raphael Rubin, I took a job at the University of Texas Medical Branch (UTMB) in Galveston, TX, which at the time was one of the top research institutions. The head of that Department of Pathology was Dr. David Walker, one of the best-known researchers in infectious diseases. I worked in the Division of Surgical Pathology led by Dr. A. Brian West, the best mentor a junior attending could have. I also took part in research activities in experimental infectious pathology with the group led by Roberto Garofalo, who turned out to be a son of exiled Italians from Istria ("esuli Italiani"), and so we became immediate friends. At first, being in academia felt like the right decision, and I did what was expected from me writing grants, teaching students and residents, writing papers and giving lectures. In the late nineties and early two thousand, new technologies started to emerge, and I was immediately drawn to their potential for the advancement of pathology. The human genome was soon "completed" and out of this effort came eventually massively parallel sequencing better known as Next Generation Sequencing (NGS) (I am skipping a lot). With that, a number of biotechnology companies mushroomed, and thus I was drawn by the siren call of private biotechnology business.

Figure 3. Members of the Division of Surgical Pathology UTMB, Galveston 1996-97. Picture is taken in front of Keiller Building which serves as home to the Department of Pathology, UTMB's internationally known World Health Organization Collaborating Center for Tropical Diseases, and the Center for Biodefense. I am second on the left, flanked by two outstanding surgical pathology fellows, Thaira Oweity and Gbo Yuoh. In the Center of the picture is Dr. A. Brian West (gentleman with the beard) who recruited me to UTMB.

14. Is it during that time that you became interested in molecular biology?

As a first year pathology resident I encountered an interesting case of a young man dying of aortic dissection (Gatalica Z, Gibas Z, Martinez-Hernandez A. Dissecting aortic aneurysm as a complication of generalized fibromuscular dysplasia. Hum Pathol. 1992 May;23(5):586-8.). At that time a team at Dr. Darwin Prockop's lab at TJU was working on hereditary diseases of collagen, and I thought that they may be interested in helping me elucidate "funny" looking collagenous proliferations in the aorta. The researchers in that group (a team led by Drs Helena Kuivaniemi and Gerard Tromp) sequenced the entire collagen type III gene and within a month or so, we had a cause for the fibromuscular dysplasia, a hitherto disease of an unknown etiology; it was a mutation that caused the disease, and it was likely hereditary. We published the findings in Journal of Clinical Investigations (https://doi.org/10.1172/JCI116490), but the funny thing is that this paper is so difficult to find (early internet era publication) that it never got attention it deserved (and you cannot find it by doing PubMed search using my name, because not all the authors are linked and I was 18th of 24 authors). Naturally, I was immediately drawn to the genome as the primary cause of many human diseases. At UTMB I had an opportunity to continue the work on the genome, this time using microarrays (human and mouse), but my interest really picked up when I joined Creighton University in Omaha, and teamed up with Henry T. Lynch, a well know clinical geneticist, who described a syndrome that still carries his name. A couple of years later, I started to collaborate with Transgenomic, Inc., a biotechnology company in Nebraska becoming their first medical director. We worked on sequencing of tumors and produced a few good papers (and of course some duds, ha-ha) but it cemented my view on the future of pathology as fundamentally a molecular discipline.

15. You reached out from your regular University based job and started working with molecular biologists in private companies. Why?

As mentioned already, my first interaction with a biotechnology company was with Transgenomic, INC., which at the time was already publicly traded. Then I hired a young assistant Dr. Jill Hagenkord to run a molecular diagnostics lab at Creighton University which quickly became a new biotechnology venture (iKaryos; Jill was the CMO and I was a Scientific Board member along with Drs Federico Monzon, Julie Bridge and Jeffrey Kant). A can-do culture of a biotechnology business was what attracted me to switch from academia to private companies. No more writing grants for a limited budget to do what you love. Instead, I found practically limitless opportunities in the private biotechnology sector. That led me to join Caris Life Sciences (CLS). In that company I worked 9 years and during that time I co-authored over 60 publications describing various aspects of cancer genomics.

16. How useful was your work in molecular biology for your future career?

Extremely important and very useful. However, I must emphasize, my involvement was always based on collaboration and teamwork. Despite interest for molecular biology, which is the most important prerequisite, it is hard to sufficiently know (and by that I mean in minute detail) all intricacies of the technology. My contribution was mostly an ability to apply, develop and validate laboratory assays for clinical usage (laboratory developed tests, LDT). Once you have this completed, the rest is "easy", just wait for the customers to order and pay for your assays. Which brings the importance of sales and marketing to the business ventures: You can have the best tests for the most important diseases, but you'll go nowhere without investments, good sales and marketing skills.

17. How difficult was it for you to give up on your academic career and join a big company like Caris?

As mentioned above, the biggest positive change was cultural. Working in the private sector is driven by financial success, and all is tied to this. In academia we frequently forget where our salaries come from; in private sector it is very clear, and if you forget from time to time, there is somebody who will remind you of "the realities of life".

18. What is Caris?

- Caris Life Sciences is one of the largest referral laboratories for precision oncology testing. Caris acquired Molecular Profiling Institute (MPI) from Phoenix's International Genomics Consortium and the Translational Genomics Research Institute (TGen), for approximately $40 million in 2007. MPI has developed several proprietary diagnostic tests to guide disease treatment based on individual patients' genomic or proteomic profiles and, in the case of cancer patients, the molecular characteristics of their tumors. Their pioneering work was published (J Clin Oncol. 2010 Nov 20;28(33):4877-83.) just before I joined Caris, and was one of my main reasons to accept their offer. The first author of that study was Daniel von Hoff, MD, one of the most influential oncologists in the US. Dan and I continue to collaborate to this day.

19. At Caris you became Executive Medical Director of Pathology. What was your "job description", or in other words what did Caris expect from you?

I took over as medical director of a division (Molecular Profiling Institute) of Caris Life Sciences, at the time of significant changes in their business model. Within 8 months of my

employment, the company was completely reorganized and all the non-molecular business (diagnostic AP services like dermatopathology, hematopathology, GI and other services) were sold to Miraca Holdings Inc. (the total purchase price was $725 million). The sole focus of the Company was shifted to precision oncology at the sole remaining lab in Phoenix where I became the first Executive Medical Director.

20. You worked at Caris for 9 years. What did you accomplish and what are you most proud off?

Team work. An incredibly smart and dedicated people worked there. Working with such a team it was very easy to be a director.

21. Caris allowed you to do quite a bit of research, and you published many papers about your work. Which of those are your most important papers i.e., contributions to science?

My most cited paper is still an academic one (Saitoh Y, Pasricha PJ, West AB, Popnikolov NK, Gatalica Z, Watari J, Obara T, Kohgo Y, and Waxman I: Prevalence and distinctive biological features of flat colorectal adenomas in a North American population. Gastroenterology 2001; 120:1657-1665). It was a true collaborative effort between gastroenterologists (from the US and Japan) and three UTMB pathologists (Nikolay Popnikolov, then a resident in pathology, today a Professor at Indiana University, A. Brian West, a first-class GI pathologist, and myself). Therein we described the importance of proper endoscopy technique and biology of flat colorectal adenomas.

I am most proud of my little study on apocrine carcinomas of the breast which I wrote as a junior surgical pathologist (Gatalica Z: Immunohistochemical analysis of apocrine breast lesions. Consistent over-expression of androgen receptor accompanied by the loss of estrogen and progesterone receptors in apocrine metaplasia and apocrine carcinoma in situ. Pathology Research and Practice 1997; 193:753-758.). It is rarely cited (about 120 times since publication), but it was my entry into the field of breast pathology. Several years later I took Semir Vranic, MD as a graduate (PhD) student in my lab at Creighton University who got interested in the topic and we wrote a few more papers together. Later, we were recognized as the lead experts for that rare type of cancer and were invited to contribute a chapter to the World Health Organization "blue book" on breast tumors, a compendium of tumor pathology that is read all over the world.

Of the Caris papers, I particularly like our work on PD-L1 and PD-1 in cancers, specifically in tumors exhibiting high microsatellite instability (MSI-H carcinomas) (Zoran Gatalica, Carrie Snyder, Todd Maney, Anatole Ghazalpour, Daniel A. Holterman, Nianqing Xiao, Peggy Overberg, Inga Rose, Gargi D. Basu, Semir Vranic, Henry T. Lynch, Daniel D. Von Hoff, and Omid Hamid. Programmed Cell Death 1 (PD-1) and Its Ligand (PD-L1) in Common Cancers and Their Correlation with Molecular Cancer Type. Cancer Epidemiol Biomarkers Prev 2014; 23(12):2965-70.) and the application of NGS technology to the measurements of microsatellite instability (Van der Walde Ari, Spetzler David, Xiao Nick, Gatalica Zoran, Marshall John. Microsatellite instability status determined by next-generation sequencing and compared with PD-L1 and tumor mutational burden in 11,348 patients. Cancer Med. 2018 Mar;7(3):746-756); These two papers help broaden the clinical utility of immune check point inhibitors (e.g., Pembrolizumab). It seems like my most talked-about publication was on the topic of cancers of unknown primary site (Gatalica Z, Millis SZ, Vranic S, Bender R, Basu GD, Voss A, Von Hoff DD. Comprehensive tumor profiling identifies numerous biomarkers of drug response in cancers of unknown primary site: analysis of 1806 cases. Oncotarget. 2014 Dec 15;5(23):12440-7). I also have high hopes that our paper on Neurotrophic Receptor Tyrosine Kinases (NTRKs) (Gatalica Z, Xiu J, Swensen J, Vranic S. Molecular characterization of cancers with NTRK gene fusions. Mod Pathol. 2019 Jan;32(1):147-153) will soon become my best cited work because tumors carrying these gene fusions respond to targeted therapy really well.

Figure 4. European Cancer Congress 2013 (ECCO-ESMO-ESTRO). Here in this picture at the news conference, I am discussing a study on the importance of molecular profiling in evaluation of cancers of unknown primary (CUP).

22. You already told us about your most cited papers. Give us some statistics please. How many citations did your papers receive so far? What is your h-index?

According to Research Gate this May, my work was cited over 12,800 times, my h-index is 60 and according to the Elsevier I am in the top 2% of world scientist based on their metrics. This last honor is certainly due to my collaborations, as almost all of the main collaborators are listed independently in the same category of scientists.

23. Your work was recognized by your peers. Thus you were invited to give many lectures and address many meetings, and travelled around the world. Which one of those events do you remember most fondly?

It must be the bi-annual meeting of the Kidney Friends, that was organized by our dear friends Ondrej Hes and Michal Michal of Pilsen, Czech Republic. Ondra prematurely died last year.

He and Michal Michal were the kindest organizers and treated everyone as their most valuable and intimate friends. This series is scientifically very important for urology specialists, and it will continue to take place in the future honoring Ondra's vision of teamwork and international collaboration.

24. Your trainee and long time collaborator, Dr. Semir Vranić, just became member of the Academy of Arts and Sciences of Bosnia and Herzegovina. Is he your most successful student and trainee or collaborator? What were the highlights of that very productive mentorship and collaboration with Dr.Vranić?

Yes, of course! Semir is by far the most successful graduate student of mine. He obtained a training grant from International Union for Cancer Research and American Cancer Society which supported his fellowship at my lab at Creighton University. From that year of hard work he and I published together 12 papers (seems to me as some sort of a record for a graduate student?). He is now an Associate Professor at the Qatar University School of Medicine in Doha. We continue to collaborate and to write papers together. Earlier this year we just submitted for publication our 59th jointly written manuscript, with 3 more projects in mind for 2023-24.

Figure 5. In front of a poster with Semir Vranić, MD, PhD, my former graduate student and long time collaborator.
na ESMO kongresu (Barcelona 2019).

25. Do you have regular contacts with your Croatian colleagues? Are you planning any joint research projects with them, conferences or publications?

Several of my classmates are now department heads and both the current and the past Dean of Medical School are my classmates. They are all wonderfully successful and have engaged me on a number of occasions. For example, I have presented research and lectured on various topics at Saltykow Memorial and Ljudevit Jurak Symposium, as well as the Croatian Oncologic Congress.

26. In your curriculum vitae you list many consultancy partnerships and advisory positions that you hold. Will you continue along that pathway or do you have other plans for the future?

I have recently retired from my position as the Director of Anatomic Pathology and the endowed James Park Dewar MD Professor at the University of Oklahoma, to pursue consultancy jobs aimed at promoting precision medicine. So, I am now consulting a couple of early start-up companies, one clinical stage privately held company and one very large publicly traded company. As you can see, it is quite a diverse group of biotechnology businesses that value my experience in the field. It wouldn't be possible to do it without first learning the ropes (in Croatian:"ispeci zanat") and for quite a long time. One, apparently, must be very patient (although patience is not my strong trait) and persistent to become recognized in however small or large a field you are working in. There are no guarantees. My young son recently asked me how does one become a consultant, because it seemed to him that this is a good position to be in. We had a long conversation, and I am not sure I fully convinced him that I have an answer for him. But it worked for me, but none of that would be possible without family support.

Figure 6. Several images from a couple of Ljudevit Jurak symposia (collage). It is always nice to meet old, and make new friends.

Figure 7. At Scipher Medicine clinical laboratory (located within Alexandria Center for Advanced Technologies) at Research Triangle Park, NC (March 2023)

Figure 8. With Biljana in San Francisco, probably our favourite US city.