Cardiovascular comorbidities in epileptology

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Abstract:

Epilepsy is one of the most common neurological diseases affecting around 50 million people worldwide. Modern scientific and professional literature recognizes comorbidities as an integral part of epilepsy, with the goal of defining optimal treatment. A series of studies from 2002 to date have confirmed a high prevalence of heart diseases in all age groups of adult patients with epilepsy, and nearly three times higher risk of malignant arrhythmias and sudden cardiac death, compared to the general population. Currently, research is increasingly being focused on elucidating the long-term connection between epilepsy and the cardiovascular system, and in 2020 the term ''epileptic heart" was first introduced, describing a heart and coronary vasculature damaged by chronic epilepsy. Plausible pathophysiological mechanisms include the cardiotoxic effects of catecholamines and repeated hypoxemia, but also the use of antiseizure medications (ASMs) associated with hyperlipidemia and arrhythmogenic effects, which could make an additional contribution to the electromechanical dysfunction of the heart. People over 60 years of age make up the largest group of patients with newly diagnosed epilepsy and represent a particular challenge for epileptologists, due to the frequent presence of multimorbidity and polypharmacy, especially in the domain of the cardiovascular system. The International League Against Epilepsy (ILAE) Task Force on Epilepsy in the elderly proposed guidelines that state that clinicians need to approach an elderly person as they would a woman of childbearing potential, and emphasize the importance of considering factors such as adverse effects and pharmacokinetic interactions when choosing ASMs, as well as the necessity for an individualized, multidisciplinary and patient-oriented approach. In addition, recent studies draw attention to the need for a routine cardiological assessment when treating patients with epilepsy, and highlight the importance of electrocardiogram (ECG) in determining the initial cardiovascular risk, as well as monitoring the impact of epileptic seizures and ASMs on the structural integrity of the heart and its vasculature.

Keywords: Epilepsy, Cardiovascular system, Antiseizure medications, Heart

Sažetak:

Kardiovaskularni komorbiditeti u epileptologiji

Epilepsija je jedna od najčešćih neuroloških bolesti od koje boluje oko 50 milijuna ljudi diljem svijeta. Suvremena znanstvena i stručna literatura prepoznaje komorbiditete kao sastavni dio epilepsije, s ciljem definiranja optimalnog liječenja. Niz studija od 2002. godine do danas potvrdio je visoku preva-

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lenciju srčanih bolesti u svim dobnim skupinama odraslih bolesnika s epilepsijom te gotovo tri puta veći rizik od malignih aritmija i iznenadne srčane smrti u odnosu na opću populaciju. Trenutačno se istraživanja sve više usmjeravaju na rasvjetljavanje dugoročne povezanosti epilepsije i kardiovaskularnog sustava, a 2020. godine prvi put je uveden pojam „epileptično srce" koji opisuje oštećenje srca i koronarne vaskulature uzrokovano kroničnom epilepsijom. Vjerojatni patofiziološki mehanizmi uključuju kardiotoksične učinke katekolamina i ponovljenu hipoksemiju, ali i upotrebu antiepileptičnih lijekova (AEL) povezanih s hiperlipidemijom i aritmogenim učincima, koji bi mogli dati dodatni doprinos elektromehaničkoj disfunkciji srca. Osobe starije od 60 godina čine najveću skupinu bolesnika s novodijagnosticiranom epilepsijom i predstavljaju poseban izazov za epileptologe, zbog česte prisutnosti multimorbiditeta i polifarmacije, posebice u domeni kardiovaskularnog sustava. Radna skupina Međunarodne lige protiv epilepsije (ILAE) za epilepsiju u starijih osoba predložila je smjernice u kojim se navodi da starije osobe treba tretirati kao žene reproduktivne dobi te se naglašava važnost razmatranja čimbenika kao što su nuspojave i farmakokinetičke interakcije pri odabiru AEL, kao i nužnost individualiziranog, multidisciplinarnog i pacijentu orijentiranog pristupa. Osim toga, novije studije skreću pozornost na potrebu za rutinskom kardiološkom procjenom pri liječenju bolesnika s epilepsijom i naglašavaju važnost elektrokardiograma (EKG) u određivanju početnog kardiovaskularnog rizika, kao i praćenja utjecaja epileptičkih napadaja i AEL na strukturni integritet srca i njegove vaskulature.

Ključne riječi: Epilepsija, Kardiovaskularni sustav, Antiepileptični lijekovi, Srce

Introduction

Epilepsy is one of the most common neurological diseases that affects about 50 million people in the world (1). Medicine has come a long way from the belief that having epilepsy means only seizures, so today modern scientific and professional literature considers comorbidities as an integral part of epilepsy, with the goal of defining optimal treatment (2). Epilepsy as a single disease is rare and about 50% of adult patients with epilepsy have at least one other associated condition, while that percentage is even higher in children (3, 4). The most common comorbidities are psychiatric disorders, mainly depression and anxiety, but numerous somatic disorders such as neurological, cardiovascular, gastrointestinal, endocrinological, and respiratory diseases are often present (3, 5, 6, 7). Here, we review the present state of knowledge of intertwined relationships between epilepsy and cardiovascular comorbidities and discuss new opportunities for improvement in clinical care.

Epidemiology

A series of studies from 2002 to date have confirmed a high prevalence of heart diseases (62-82%) in all age groups of adult patients with epilepsy, which present a major cause of death in this population (8, 9, 10). The Amsterdam Resuscitation Studies (ARREST) included more than 3000 subjects and they reported that the risk of fatal arrhythmias and cardiac arrest was almost 3-fold greater in people with epilepsy compared to the general population, which was further increased if the patients had symptomatic epilepsy (11, 12). Sudden cardiac death (SCD) constitutes a 4.5-fold greater risk for premature death in patients with epilepsy compared to sudden unexpected death in epilepsy (SUDEP), which by definition excludes all known causes of mortality, including cardiac comorbidities. In a community-based study, Stecker and colleagues determined that in about two-thirds of the cases of SCD in patients with epilepsy, there was no apparent temporal relationship between a seizure and the cardiac event (13). Post-mortem findings suggest that, at least in some cases, SCD and SUDEP present two overlapping entities (14). Zack and Luncheon reported that patients with epilepsy developed heart diseases, such as angina pectoris, coronary heart disease, and myocardial infarction, at an accelerated rate than individuals without epilepsy, with the greatest difference, percentage-wise, observed in patients between 45 and 64 years of age (15). Epidemiological studies have also shown that the incidence of myocardial infarction was greater in patients with epilepsy (16, 17).

Structural cardiovascular abnormalities and arrhythmias in epilepsy

Up til now, transient changes in cardiac function during interictal or peri-ictal phases, such as ictal tachycardia, ictal asystole, and postictal asystole, have been extensively studied (18, 19). However, in line with previous observations, research is increasingly being focused on elucidating the long-term connection between epilepsy and the cardiovascular system. In 2020 Verrier and colleagues first proposed the concept of the ''epileptic heart", defined as "a heart and coronary vasculature damaged by chronic epilepsy as a result of repeated surges in catecholamines and

hypoxemia leading to electrical and mechanical dysfunction". Interictal autonomic dysfunction, such as decreased heart rate variability (HRV), as well as repeated seizures, especially generalized tonic-clonic seizures (GTCS), cause an excess of catecholamines and myocardial ischemia that lead to electrical instability and arrhythmogenesis with a potentially fatal effect (14). Echocardiographic studies found that patients with temporal lobe epilepsy exhibited higher left ventricle stiffness, left ventricle filling pressure, and greater left atrial volume as well as markers of autonomic dysfunction than healthy matched controls (20). Liu et al reported altered echocardiography parameters reflecting systolic and diastolic dysfunctions in patients with epilepsy without any underlying cardiovascular disease, compared to healthy controls, such as decreased left ventricular ejection fraction (LVEF) and prolonged isovolumic relaxation time (IVRT), which are associated with cardiovascular morbidity (21). A higher burden of cardiovascular risk factors observed in patients with epilepsy could additionally contribute to structural heart disease, including obesity, physical inactivity, smoking, and poor metabolic profile (22, 23, 24). Recent molecular findings based on animal studies have revealed that epilepsy might secondarily lead to acquired cardiac channelopathies which can further increase arrhythmogenesis (25). In addition to numerous investigations on sudden cardiac events that support the concept of ''epileptic heart", in 2023 Wang and colleagues published the first study focused on investigating the connection between epilepsy and the long-term risk of cardiac arrhythmias (26). They revealed a higher risk of all cardiac arrhythmias in people with epilepsy, including atrial fibrillation, bradyarrhythmias, ventricular arrhythmias, and other types of arrhythmias. The risk was even higher in those using anti-seizure medications (ASMs). In a large survey with over 1.4 million patients with epilepsy done by Desai et al, it was found that nearly one-quarter of patients had some cardiac arrhythmias, with atrial fibrillation being the most common one (27).

Antiepileptic therapy and the cardiovascular system

ASMs also play an important role in the pathogenesis of cardiac conditions in epilepsy by several mechanisms. They have been described as independent risk factors for SCD even in individuals without epilepsy (28, 29). Sodium channel-blocking agents, such as carbamazepine, phenytoin, lacosamide, and lamotrigine, have been studied the most, and numerous studies have described their side effects like arrhythmias or conduction abnormalities (28, 30). Wang et al concluded that the use of carbamazepine and valproic acid carried the highest risk of cardiac arrhythmias of all ASMs (26). They are also known to cause weight gain which induces metabolic syndrome, further increasing cardiovascular risk. Moreover, enzyme-inducing ASMs, such as carbamazepine, phenobarbitone, and phenytoin, negatively affect lipid profiles which results in accelerated atherosclerosis and a higher risk of cardiac ischemic disease (31, 32). Renoux and colleagues showed that the use of inhibiting ASMs was associated with a decreased risk of myocardial infarction (33). Additionally, studies have found that both adults and children taking ASMs had higher carotid intima-media thickness and epicardial adipose tissue thickness compared to the healthy control group (34, 35). In pharmacoresistant patients, vagus nerve stimulation (VNS) presents a frequently used therapeutic method that has documented success in seizure reduction, although its exact mechanism of action is still unknown (36). VNS-induced cardiovascular complications have rarely been reported (37, 38, 39). Conversely, the current state of knowledge suggests that VNS exhibits a significant cardioprotective effect by two separate mechanisms: affecting the central nervous system leading to seizure reduction, and direct influence on the heart leading to a decrease in its electrical instability (40).

ECG findings in epilepsy

Cardiac repolarization abnormalities are common in patients with epilepsy. This may be caused by structural cardiomyocyte lesions, changes in their ion channel expressions, and sympathovagal imbalance, manifested as decreased HRV, which has been described as one of the possible markers of increased risk for both SUDEP and SCD (41, 42). People with epilepsy express different ECG measures compared to healthy people. QT interval (corrected for heart rate QTc) prolongation and dispersion are more frequently seen in people with epilepsy, which is associated with an increased risk of ventricular arrhythmias (10, 43, 44). T wave alternans (TWA) is one of the most studied markers of cardiac repolarization. It is defined as a microvolt-level beat-to-beat fluctuation in ST-segment or T-wave morphology and is an important predictor of SCD (45, 46). 82% of patients with epilepsy have elevated TWA values that are dependent on the duration of epilepsy, meaning that patients with chronic epilepsy display higher TWA values compared to the newly diagnosed ones (46, 47). Furthermore, TWA is influenced by the pro and antiarrhythmic effects of drugs, as well as VNS which was shown to significantly reduce TWA (40).

ASMs, multimorbidity and polypharmacy

The highest incidence of developing new-onset epilepsy occurs in people aged 60 or more (48). The treatment of the elderly population represents a special challenge for epileptologists due to age-related changes in pharmacokinetics, as well as the frequent presence of multimorbidity and polypharmacy, especially in the domain of the cardiovascular system. These occurrences are an important factor when deciding on the most suitable treatment. Bruun and colleagues showed that more than two-thirds of patients (69%) with epilepsy, who were 65 or older, had six or more medications as part of their therapy regime, in addition to ASMs (49). About 30% of cases of newly diagnosed epilepsy

in the elderly are stroke-related, followed by other causes such as tumors, dementia, and trauma (50). ASMs display numerous interactions with other drugs frequently used by this population, such as antiarrhythmics, antihypertensives, statins, oral anticoagulants, and antiplatelet medications. This especially refers to potent hepatic enzyme inducers, such as carbamazepine, phenobarbital, phenytoin, and primidone, that can decrease the levels of concomitantly administered medications. The most significant interactions with the drugs from the ATC C drug section were described with ivabradine, ranolazine, felodipine, nicardipine, verapamil, hydrochlorothiazide, as well as simvastatin and atorvastatin (51). As previously mentioned, sodium channel blockers are known to potentially trigger or worsen conduction abnormalities and arrhythmias (28, 30). Valproate and pregabalin have been linked to heart failure exacerbation, and a preference for levetiracetam and lamotrigine in those conditions was given (52, 53). In the PROPOSE study conducted by Tanaka et al, it was concluded that newer-generation ASMs (levetiracetam, lacosamide, zonisamide, perampanel, gabapentin, topiramate) showed great advantages and superiority over older-generation ASMs (carbamazepine, valproate, phenytoin, phenobarbital, clonazepam, clobazam) in the secondary prevention of post-stroke epilepsy, due to better seizure control, less serious adverse effects and less interference with other drugs (54). The use of novel oral anticoagulants (NOACs) among adults with epilepsy has rapidly increased in the last decade (55). In the 2021 European Heart Rhythm Association Practical Guide, no relevant interactions with NOACs were described with lamotrigine, lacosamide, and zonisamide. However, the use of valproate was contraindicated due to reduced NOAC plasma levels, whereas levetiracetam and carbamazepine were advised to be used with caution and careful monitoring for bleeding, as summarized in Table 1 (56). Considering all the above, the International League Against Epilepsy (ILAE) Task Force on Epilepsy in the elderly issued practical guidelines that state that the elderly should be treated as women of reproductive age and emphasize the importance of considering factors such as adverse events and pharmacokinetic interactions when choosing an ASMs, as well as the necessity of an individualized, multidisciplinary and patient-oriented approach (57).

*Table 1. Interactions of NOACs with ASMs**

ASMs	Interactions with NOACs
Carbamazepine	
Lacosamide	
Lamotrigine	
Levetiracetam	
Valproate	
Zonisamide	

Legend for Table 1.

- No relevant interactions
- Use with caution
- Contraindicated

*Adapted from Steffel J, Collins R, Antz M, Cornu P, Desteghe L, Haeusler KG et al. 2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation. Europace. 2021 Oct 9;23(10):1612-1676.

Conclusion

Cardiovascular comorbidities in epilepsy are common and result in poorer clinical outcomes. Although they are gaining increasing importance, most of the underlying pathophysiological mechanisms are still unknown. Early identification and adequate treatment of cardiovascular disorders is imperative in the treatment of patients with epilepsy and requires a change in the way epilepsy is perceived by clinicians. Routine cardiological evaluations should be incorporated into the management of these patients. ECG can be a useful tool in the assessment of the initial cardiovascular risk, as well as in determining the impact of ASMs and epileptic seizures on heart function. Risk factors and comorbidities must be taken into account when choosing ASMs, whose potential adverse effects need to be closely monitored. The clinical care of patients with epilepsy needs to include a personalized and holistic approach.

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