

Neonatal Seizures

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ABSTRACT:

Neonatal convulsions may be the first, in some cases, the only clinical sign of neonatal central nervous system disorder. As such, they require prompt evaluation to determine the cause, as the underlying may have influential causes. Furthermore, since they may contribute to further brain injury, they require immediate treatment. Neonatal convulsions have unique clinical features and their presentation differs from convulsions in older children. They may include focal clonic, focal tonic, myoclonic and epileptic spasms. Furthermore, they may present with abnormal eye movements, lip smacking, swimming or pedaling movements, or apnea. Moreover, nonconvulsive paroxysmal movements are also common in the neonatal population and are sometimes difficult to distinguish from convulsions. Continuous electroencephalogram is the gold standard (cEEG) for the detection of neonatal convulsions. In addition to continuous electroencephalogram (cEEG), amplitude EEG (aEEG) is a useful bedside tool. Neonatal convulsions carry a high risk for early mortality, but are also a negative predictive factor for the development of motor and cognitive disorders and epilepsy.

KEYWORDS: seizures, newborn, neonatal seizures, electroencephalography, epilepsy, developmental disability

SAŽETAK:

NEONATALNE KONVULZIJE

Neonatalne konvulzije mogu biti prvi, u nekim slučajevima i jedini klinički znak poremećaja središnjeg živčanog sustava u novorođenčadi. Kao takve zahtjevaju promptnu evaluaciju u svrhu određivanja uzroka jer u podlozi mogu biti uzroci na koje se može utjecati. Nadalje, s obzirom da mogu pridonijeti daljnjoj ozljedi mozga, zahtjevaju neodgodivo liječenje. Neonatalne konvulzije imaju jedinstvene kliničke značajke te se njihova prezentacija razlikuje od konvulzija kod starije djece. Mogu uključivati fokalne kloničke, fokalne toničke, miokloničke i epileptičke spazme. Nadalje, mogu se prezentirati abnormalnim pokretima očiju, pokretima mljackanja, plivajućim ili pedalirajućim pokretima ekstremiteta ili apnejom. Štoviše, nekonvulzivni paroksizmalni pokreti također su česti u neonatološkoj populaciji i ponekad ih je teško razlikovati od konvulzija. Kontinuirani elektroencefalogram je zlatni standard (cEEG) za detekciju neonatalnih konvulzija. Osim kontinuiranog elektroencefalograma (cEEG), amplitudni EEG (aEEG) je koristan i praktičan alat za dijagnozu neonatalnih konvulzija. Neonatalne konvulzije nose visoki rizik za ranu smrtnost, ali su i negativni prediktivni čimbenik za razvoj motoričkih i kognitivnih poremećaja te epilepsije.

KLJUČNE RIJEČI: konvulzije, novorođenče, neonatalne konvulzije, elektroencefalogram, epilepsija, poremećaji razvoja

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Neonatal convulsions are often a manifestation of a significant neurological disease, but also a predictor of adverse neurological outcomes in the newborn. Rapid diagnosis, detection of causes and prompt intervention are necessary to minimize cardiorespiratory instability and correct treatable causes of seizures. Seizures are generally defined as synchronous excess discharge (depolarization of neurons in the brain). This definition may be too restrictive when applied to neonatal convulsions. According to some authors, it would be more appropriate to define neonatal convulsions as paroxysmal changes in neurological function (behavioral, motor, or autonomic). This definition covers both clinical changes that correlate with epileptiform abnormalities on EEG but also stereotypical, paroxysmal activities that are not clearly related to changes in EEG¹. The incidence of neonatal convulsions is estimated to be 1-5 per 1000 births²⁻⁴. However, these studies do not take into account the low sensitivity of the clinical diagnosis of convulsions alone, and continuous prolonged electroencephalogram is not widely available. Therefore, the true incidence of neonatal convulsions remains unknown, which is probably even higher than estimated⁵⁻⁶. Compared to older children, clinical presentation and EEG findings in infants are significantly different as a consequence of the immature stage of brain development. Furthermore, neonatal convulsions are rarely idiopathic. The differential diagnosis of neonatal convulsions is broad, and includes structural, metabolic and genetic causes. Acute symptomatic causes including hypoxic-ischemic encephalopathy, infections, intracranial hemorrhage, transient metabolic disorders or thrombosis are much more common causes than neonatal onset epilepsies that may be due to malformations or are genetically conditioned. Rare causes include congenital metabolic defects, B6 vitamin deficiency epilepsies, and neonatal epilepsy syndromes, but these must be considered in the case of refractory seizures⁷⁻⁸. Neonatal convulsions carry a high risk of early mortality, with motor and cognitive disorders as well as epilepsy often resulting in survivors⁹. 85 percent of neonatal convulsions are thought to be “symptomatic”, hence, the consequences of a specific identifying cause. These causes are generally categorized as: neonatal encephalopathy, structural brain injury (including ischemic and hemorrhagic stroke), metabolic disorders (glucose and electrolyte abnormalities), and systemic and central nervous system infections¹⁰⁻¹⁴. Epilepsy syndromes account for the remaining 15 percent of all neonatal convulsions. Examples of epilepsy syndromes include benign familial neonatal epilepsy, early (neonatal) myoclonic encephalopathy, and early infantile epileptic encephalopathy. Neonatal convulsions have unique clinical features compared to convulsions in older infants and children. An immature brain is more prone to convulsion initiation, convulsion maintenance, and expansion¹⁵. Neonatal convulsions are focal (unifocal or multifocal), rarely generalized. The clinical manifestations of neonatal convulsions are focal-clonic, focal-tonic, myoclonic and epileptic spasms. Nonconvulsive paroxysmal events are very common in

the neonatal population and are sometimes difficult to distinguish from convulsions. Most of neonatal convulsions are subclinical, hence, without clinical manifestation^{14, 16-20}. Unless the convulsive discharges originate or migrate in the motor cortices, they will not be clinically visible as abnormal movement. This is especially seen in immature premature infants. Focal-clonic convulsions consist of repetitive, rhythmic contractions of specific muscle groups of the extremities, trunk, or face. They have clinical correlation on EEG. Compared to non-convulsive movements such as clonus or tremor, movements in focal-clonic convulsions are more slower and rhythmic. They differ from tremors and clonus in that they cannot be stopped when grasping the extremities. Tremor and clonus can be stopped by gripping parts of the body, and tonic-clonic convulsions cannot, so muscle twitching can be felt in the affected limb. If all four extremities are affected, the appearance of generalized convulsions can be obtained, but careful examination reveals that the extremities do not move synchronously. Focal-tonic convulsions are rarer and are characterized by sustained but transient asymmetrical posture of the trunk or extremity and tonic deviation of the eyes. In term newborns, when the eyes are affected, conjugate deviation of the eyes is observed to one side. Focal-tonic convulsions also correlate with EEG. Tonic convulsions are a hallmark of several neonatal epilepsy syndromes (e.g., Ohtahara syndrome, KCNQ2 encephalopathy). Myoclonic convulsions in infants represent a diverse range of movements, some of which are epileptic in origin and others non-epileptic. Movements in myoclonic convulsions are characterized by contraction of muscle groups of well-defined regions: proximal or distal limbs, whole limbs, trunk, diaphragm or face. Myoclonic events differ from clonic convulsions at the correct rate of recurrence. Some forms of myoclonic seizures are correlated with EEG, others do not. This is because some myoclonic convulsions are generated at the cortical level, while others are generated more caudally in the subcortical structures, limbic system, brainstem, spinal cord, or neuromuscular junction. Some myoclonic convulsions can be provoked by stimulation and suppressed by trapping the extremity or repositioning the body. Epileptic spasms are rare in infants and primarily involve the trunk muscles and limbs. Neonatal convulsions may be manifested by symptoms of the autonomic nervous system, such as changes in heart rate, respiration, blood pressure, salivation or dilation of the pupils²¹⁻²³. However, their isolated appearance is rare and usually occurs with other motor manifestations of convulsions²⁴⁻²⁵. Apnea can also be a clinical manifestation of neonatal convulsions. It is sometimes difficult to distinguish neonatal convulsions from nonconvulsive paroxysmal events or normal newborn behavior, and EEG is required to differentiate them. Clinical observation is inadequate for the correct diagnosis of neonatal convulsions. Neonates with subclinical seizures will not receive adequate therapy without EEG findings, while those with paroxysmal events that are not convulsive will be exposed to

unnecessary medication. Examples of non-convulsive events include various motor automatisms and tonic posture. These events are based on the physiology of reflexes^{24,26}. Other paroxysmal events in the newborns that may be confused with convulsions are tremor, tremor or clonus. Nonconvulsive events do not have correlations or changes in EEG, they can sometimes be triggered by stimulation of the newborn, and can typically be suppressed by grasping or repositioning part of the body²⁴⁻²⁶. Normal neonatal behaviors include stretching, non-specific random movements that may be sudden (especially in premature newborns), random sucking movements. The infant may normally have physiological myoclonus during active sleep²⁷. In healthy newborns, the myoclonus disappears when the newborn is awake, appearing exclusively in sleep. The use of EEG has shown that not all clinically suspected events are convulsive and that most convulsions are actually subclinical. Therefore, the diagnosis of neonatal convulsions is primarily based on the EEG. Neonatal convulsions are defined as an abnormal EEG pattern involving an amplitude of > 2 microvolts and lasting longer than 10 seconds²⁸. "Electro-clinical convulsions" occur when clinical convulsions overlap temporarily with an abnormal EEG record. "Subclinical convulsions" are convulsions that are confirmed on the EEG without any associated clinical signs. Clinical events that have no correlation on the EEG record are not convulsions. The gold standard for the diagnosis of neonatal convulsions is multichannel video EEG monitoring²⁹. A routine 60-minute EEG recording is considered insufficient to screen neonatal convulsions. For infants at high risk for convulsions, the American Clinical Neurophysiology Society recommends EEG monitoring for 24 hours²⁹. If convulsions are not verified within 24 hours, recording may be interrupted. Exceptions are neonates with hypoxic-ischemic encephalopathy (HIE) who are on therapeutic hypothermia^{29,30}. If convulsions are identified, recording will continue until the infant has no convulsions for 24 hours. When video-EEG monitoring is not available, routine EEG recording with simultaneous observation by a clinician or EEG technician may provide important information. The third option is amplitude-integrated EEG (aEEG) with 1 or 2-channel EEG. aEEG is not an adequate replacement for multi-channel EEG video. All electrographic convulsions cannot be detected by this modality due to limited scalp coverage³¹, low amplitudes and slow frequencies of typical seizures³². Artifacts can also present a problem. The sensitivity and specificity of the examination ranges from 25 to 80 percent^{32,33}. However, if continuous EEG or standard EEG is not available, aEEG may be a useful tool³⁴. If a diagnosis of neonatal convulsions is made, the etiology needs to be identified. Possible risk factors for axonal injury such as fetal cardiac decelerations, presence of meconium, low Apgar value and placental abnormalities need to be identified. Other risk factors include macrosomal infant, maternal obesity and abnormal fetal presentation. The anamnesis should include information on possible previous maternal miscarriages (congenital anomalies), gestational diabetes (neonatal hypoglycaemia), sexually

transmitted diseases or other infections (neonatal transmission of infection), information on maternal diseases during pregnancy (fever and maternal rash may suggest viral infections), data on taking illicit substances, data on thromboses or coagulopathies (neonatal stroke). The family history must include information about eventual mortality of an unknown cause in the family or relatives, and information on consanguinity (inherited metabolic disorders), the presence of epilepsy in the family, especially neonatal (benign familial neonatal epilepsy). The examination should include evaluation of vital signs, measurement of head circumference, presence of birthmarks, somatic abnormalities, dysmorphism of the face or signs of infection (strained fontanella suggests meningitis, rash in TORCH infection), mental status, state of consciousness, cranial nerve examination, presence of asymmetry in spontaneous movements or abnormal tone (structural brain lesion or neonatal encephalopathy). Typical presentation of inherited metabolic disorders include feeding difficulties, respiratory distress and lethargy that occur several days after the initial symptom-free period. Hypoglycemia and acidosis should also arouse suspicion of inherited metabolic disorders. Some infants present with isolated convulsions. Signs of systemic or central nervous system infection in the newborn may be nonspecific. If infection is suspected, cultures should be taken and antibiotic therapy should be initiated at the dose recommended for the treatment of meningitis, possibly including acyclovir according to clinical judgment. Lumbar puncture is recommended in cases of positive culture and in cases of suspected sepsis, since clinical signs may be absent in cases of central nervous system infection in the newborn, and infection is one of the most common causes of neonatal convulsions. In cases of refractory convulsions, lumbar puncture is also recommended to rule out inherited metabolic disorders. MRI is the recommended imaging examination that should be performed with all neonatal convulsions to evaluate the presence of intracranial hemorrhage, ischemic stroke, brain malformations, or the presence of hypoxic-ischemic damage. If the infant is unstable or unable to adjust for MRI, then transcranial ultrasound should be performed to evaluate the presence of intracranial hemorrhage or hydrocephalus. CT is not recommended in newborns^{29,30}. Genetic testing is recommended for newborns with epilepsy who have not identified an acute symptomatic cause based on history, clinical examination and neuroradiological imaging. The most common genetic cause is KCNQ2 encephalopathy. It is recommended to use genetic panels for epileptic encephalopathies and brain malformations, or to screen the entire genome instead of testing for single mutations. Neonatal convulsion therapy must be directly targeted at the cause to prevent further brain damage. This is especially important for convulsions associated with inherited metabolic disorders. Neonatal encephalopathy (hypoxic-ischemic encephalopathy) is the most common cause of neonatal convulsions¹⁴. Newborns with convulsions should be presumed to have an infection until proven otherwise. Central nervous system infection is a relatively

common cause of neonatal convulsions, and when convulsions occur, broad-spectrum antibiotics should be included at the dose recommended for the treatment of meningitis. Metabolic disorders are a correctable cause of neonatal convulsions. Hypoglycaemia must be corrected without delay with a 10% glucose solution intravenously at a dose of 2 ml/kg in a bolus and then continued, depending on gestational age, in an infusion up to a maximum dose of 8 mg/kg/min. Hypocalcaemia is corrected with a solution of 10% calcium gluconate at a dose of 100 mg/kg or 1 ml/kg, respectively, intravenously for 10 minutes, monitoring the heart rate and infusion site. The dose may be repeated in 10 minutes if there is no clinical response. Alternatively, calcium chloride at 20 mg/kg or 0.2 ml/kg may be administered. After the initial correction, calcium should be added to the infusion solution. Neonatal hypomagnesaemia is most commonly associated with hypocalcaemia. It is corrected with a solution of 50% magnesium sulfate at a dose of 125 mg/kg or 0.25 ml/kg intramuscularly. The dose may be repeated for 12 hours until normomagnesaemia is established. Pyridoxine-dependent epilepsy (PDE) is a rare genetic cause of refractory neonatal convulsions. In infants with seizures who do not respond to conventional anticonvulsant therapy, especially if the cause of seizures has not been established, PDE should be considered. It is recommended that pyridoxine be given intravenously at a dose of 100 mg / kg. The dose may be repeated at intervals of 5 to 15 minutes to a total maximum dose of 500 mg. Alternatively, pyridoxine can be administered at a dose of 15 to 30 mg/kg per day orally divided into three doses. Continuous EEG and cardiopulmonary monitoring is required during therapy, given that there is a risk of apnea. After initial care of the airway and cardiovascular support with etiologically-specific treatment, the next decision is the eventual introduction of anticonvulsant drug therapy. There are no scientifically established or widely accepted guidelines for the medical treatment of neonatal convulsions, and the approach is based on a limited number of clinical trials, observational studies and clinical experience^{35,36}. Neonatal convulsions resulting from reversible electrolyte or glucose disorders do not require the immediate introduction of anticonvulsant therapy, while some other causes, especially if the convulsions are prolonged, presumably lead to the introduction of anticonvulsant drug therapy. In the past, there was an attitude to treat clinically evident convulsions. Such an approach is debatable because in this way newborns with paroxysmal events (not convulsions in reality) are often exposed to unnecessary anticonvulsant medications, whereas infants with subclinical convulsions, on the other hand, will not receive adequate anticonvulsant therapy. Experts recommend the treatment of clinical and subclinical convulsions because the only difference between them may be cortical distribution. It should be noted that after initial treatment in infants with convulsions, electroclinical dissociation may occur, therefore clinically noticeable signs of convulsion disappear, but electrographic (EEG) convulsions persist^{24,37}. Ideal treatment would therefore involve resolution of electrographic

convulsions. In case the convulsions persist for longer than expected, the possible etiology should be re-evaluated. For example, neonatal convulsions associated with hypoxic-ischemic encephalopathy should be withdrawn after a few days, and if they persist, possible metabolic disorder or neonatal-onset epilepsy should be considered. Phenobarbital has long been used as the first line of therapy for the treatment of neonatal convulsions^{14,38-40}. It is eliminated via the liver and kidney, therefore, in newborns with impaired liver and kidney function, such as in hypoxic-ischemic encephalopathy, it can be toxic at normal doses. Also, the half-life of phenobarbital is higher in preterm newborns compared to term newborns so that standard dosing can result in toxicity. Measurement of serum concentration is useful when conducting phenobarbitone therapy^{41,42}. The initial dose of phenobarbital is 20 to 30 mg/kg intravenously. Unless the convulsions persist after the initial dose, the bolus dose of 10 to 20 mg/kg may be repeated up to a total daily dose of 50 mg/kg. The initial dose is followed by a maintenance dose of 4 to 6 mg/ kg/day divided into two doses. Another commonly used drug for the treatment of neonatal convulsions is phenytoin. Neither of these two medicines is fully effective nor is more effective than the other⁴³. The most common formulation of phenytoin used is fosphenytoin because of its lower risk of side effects than classical phenytoin. The initial dose of phenytoin is 20 mg/kg. The following is a maintenance dose of 4 to 6 mg/kg divided into two daily doses. Fosphenytoin is dosed in the same way as phenytoin, but doses are expressed in phenytoin equivalents (1 PE = 1 mg phenytoin). Side effects to keep in mind are hypotension and cardiac arrhythmias. Midazolam can also be used in acute treatment. It is initially given in a bolus at a dose of 0.15 mg/kg followed by continuous infusion, initially 1 mcg/kg/min followed by a dose rise until effect is achieved⁴⁴. Neonatal convulsions that are refractory to phenobarbital generally have a weaker response to another line of anticonvulsant drugs. The drugs most commonly used as a second line of treatment are phenytoin / fosphenytoin, levetiracetam, lidocaine and midazolam. Recently, levetiracetam has been frequently used, which according to some studies has a neuroprotective effect⁴⁵. Given the pharmacokinetics of levetiracetam in infants is not fully known, the range of recommended dosage in the literature is very wide (10 - 60 mg/kg/day). However, when used with refractory convulsions, an initial dose of 60 mg/kg intravenously is recommended, followed by a maintenance dose of 40 to 60 mg/kg daily divided into two or three daily doses^{46,47}. Lidocaine is also used as second line drug. The contraindications for the administration of lidocaine are congenital heart defects and pre-treatment with phenytoin⁴⁸. Lidocaine is initially administered at a bolus dose of 2 mg/kg for 10 minutes followed by continuous infusion at 7 mg/kg/h for 4 hours. The dose is then reduced by 50 percent every 12 hours over the next 24 hours. Intravenous lidocaine administration may be arrhythmogenic and requires continuous non-invasive monitoring. To reduce the risk of arrhythmias, the maximum administration time of lidocaine is 48 hours, according to some

publications, it is recommended to use less than 30h^{48,49}. Continued administration of midazolam should be considered in newborns with epilepticus status⁴⁴. There are no clearly defined criteria that would determine the length of administration of anticonvulsant therapy after control of acute symptomatic convulsions has been established. Since acutely symptomatic convulsions usually recede within three days and usually do not occur afterwards, there is a trend of early discontinuation of anticonvulsive therapy, sooner or shortly after discharge of the newborn from hospital^{50,51}. With regard to chronic therapy, the length of treatment allegations vary from one week to 12 months after the onset of recent convulsions^{52,53}. Contrary to acute symptomatic convulsions, neonates with epilepsy are however advised to have continuous anticonvulsant therapy because of the risk of recurrence. For this purpose, phenobarbital at a dose of 3 to 6 mg/kg per day is usually used, with serum concentration measured. There is some research citing the potential benefit of the use of carbamazepine in the treatment of neonatal epilepsy associated with pathological variants of KCNQ2 and KCNQ3^{54,55}.

CONCLUSION

Unlike older children, in neonates the clinical presentation of

neonatal convulsions and EEG findings are significantly different as a result of the immature stage of brain development. Neonatal convulsions are usually focal, rarely generalized. Furthermore, in contrast to adult convulsions, neonatal convulsions are symptomatic in 85% of cases, or the result of some identifiable cause. The most common cause of neonatal convulsions is hypoxic-ischemic encephalopathy. Central nervous system infection is also a relatively common cause of neonatal convulsions. In order to rule out intracranial hemorrhage, brain MRI or transcranial ultrasound should be performed. Most neonatal convulsions are subclinical therefore clinical assessment is not sufficient to diagnose neonatal convulsions. Nonconvulsive paroxysmal events can often be mistaken for convulsions. Therefore, the gold standard for the diagnosis of neonatal convulsions is a continuous electroencephalogram (cEEG). If cEEG is not available, amplitude EEG (aEEG) is a useful and practical tool. Neonatal convulsion therapy must be directly directed to the cause. Neonatal convulsions resulting from reversible electrolyte or glucose disorders do not require the immediate introduction of anticonvulsant therapy, while some other causes, especially if the convulsions are prolonged, presume the introduction of anticonvulsant drug therapy.

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