

## NEONATAL SEIZURES: ETIOLOGY, TREATMENT AND PROGNOSIS

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**Abstract: Introduction:** Seizures are one of the most common pathologies in newborns. Their incidence is 1.5–3.5/1000 for term infants and 10–130/1000 for preterms. The most common causes of seizures in term infants are hypoxic-ischemic encephalopathy (HIE), cerebrovascular insult (CVI), cerebral malformations (CM), and metabolic disorders. For preterm infants: intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL) and infections. Clinical characteristics are diverse and subtle, and sub-clinical forms are common. The drug of the first choice is phenobarbitone. Newborns with seizures are more prone to developing neurological disturbances such as epilepsy and cerebral palsy.

**Methods:** This is a clinical, observational research, one-year, retrospective, cross-sectional study conducted in the Department of neonatal intensive care and neonatology of the Clinic of Pediatrics KCUS. The study included 43 newborns who met the inclusion criteria.

**Results:** We found that 7.19% of hospitalized newborns had seizures. A number of seizures were recorded in the group of term infants with an earlier time of seizures. The most common etiological causes were: HIE, IVH, infections, and CM. There was a frequent occurrence of metabolic disorders such as acidosis, blood sugar, and mineral (Ca, K, Na, and Mg) disorders. The median of the first day of onset of seizures in full-term infants is on the fourth day, while in premature infants it is on the sixth day of life. Phenobarbitone was mainly used to stop seizures, with great success. Overall mortality in children with seizures was 37.21%.

**Conclusions:** Seizures are common in newborns, which, depending on the etiological cause, increase mortality, especially in preterm infants. Seizures in term infants occur earlier than in premature infants. The most common etiology of seizures in term infants are infections, hypoxic-ischemic encephalopathy,

intracranial hemorrhage, cerebral malformations, and cerebrovascular insult. In premature infants these are hypoxic-ischemic encephalopathy, intracranial bleeding, and infections. In the initial treatment of neonatal convulsions, phenobarbitone is most often used, which has proven to be successful in the majority of cases.

**Keywords:** neonatal seizures, etiology, treatment, prognosis, mortality.

### INTRODUCTION

Neonatal seizures are one of the most common phenomena that are considered a consequence of the sensitivity and vulnerability of the brain during rapid growth and development, as well as the effects of many harmful factors (1, 2). They can be associated with long-term neurological consequences, an increased risk of developing epilepsy, cerebral palsy, intellectual disability, and/or learning disabilities (3). Acute symptomatic seizures are defined as a consequence of acute brain injuries, such as stroke, trauma, or brain infection, while provoked seizures are defined as a consequence of transient and reversible changes in brain function of metabolic or toxic origin (1). Although rare, unprovoked neonatal seizures may occur, which may be secondary to structural abnormalities of the brain, which would correspond to structural epilepsies or genetic conditions (1). Clinically, neonatal seizures are described as abnormal, stereotyped, paroxysmal, and recurrent dysfunctions in the central nervous system (CNS), which occur in the first 28 days after birth in term infants or before 44 gestational weeks in preterm infants (2, 4, 5).

Seizures occur most often in the neonatal period, especially in the first week of life, more often than in other periods (4, 5). The incidence is 1.5 - 3.5/1000 for term newborns and 10 –(130/1000 for preterms (5, 6). Etiological factors that can lead to seizures in new-

borns are diverse and can be divided into perinatal, genetic, vascular, infectious, metabolic, and seizures associated with malformations, drugs, and seizures of unknown cause (2, 6). The etiology of neonatal seizures is different in term and premature infants (5). Hypoxic - ischemic encephalopathy (HIE), cerebrovascular insult (CVI), cerebral malformations (CM), and metabolic disorders are the main causes of seizures in term infants (5). In premature infants, some of the main causes are intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), and infections (5). Determining the etiological factor is extremely important because some of them require immediate treatment but also affect the prognosis of the disease (7). According to the revised ILAE classification from 2017, seizures can be classified through several levels, where the first level of the epilepsy classification framework is the type of seizure and is divided into focal onset, generalized onset, and unknown onset (8). The second level of classification represents the type of epilepsy, and it is divided into generalized epilepsy, focal epilepsy, a combination of generalized and focal epilepsy, and unknown epilepsy (8). According to the 2021 modification of the ILAE classification, infantile-onset epileptic syndromes are divided into two large groups: self-limited epileptic syndromes, where spontaneous remission is likely to occur, and developmental epileptic encephalopathy (DEE), where there is impairment in development (9).

Clinical picture: obvious manifestations of neonatal seizures occur only in a small number of newborns due to their immature CNS. Brain connections are less developed, so seizures may not spread to the motor cortex, which would lead to outwardly visible signs of epileptic seizures (10). Clinical signs of neonatal seizures may be subtle or even absent. Also, infants may exhibit frequent proximal movements such as rapid eye movements, automatism, and sleep-related myoclonus, which may mimic seizures (10). Clinical signs are often focal and include limb or facial movements that may be clonic, myoclonic, or tonic (10).

More types of clinical neonatal seizures that are more difficult to detect are the so-called "subtle" seizures and they account for 50% of all seizures (10, 11). They are more common in preterm than in term children (2). They include eye movements and autonomic signs of seizures represented by tachycardia, bradycardia, or apnea (10).

Tremors and other non-convulsive movements should be distinguished from neonatal seizures (3). Characteristics that help in differentiation are the absence of abnormal eye movements, which can be provoked by stimulating the child, can be stopped by mild passive flexion of the limbs, there are no EEG abnor-

malities, they are not associated with tachycardia, bradycardia, or hypertension (2).

Diagnosis and treatment: The diagnosis is made based on the clinical picture, anamnestic data, and EEG. Due to the growing body of evidence that neonatal seizures contribute to an unfavorable neurodevelopmental outcome, the focus is increasingly on early detection and treatment. In treatment, phenobarbital is the first drug of choice. The initial intravenous dose is 20 mg/kg, which is usually given for 10 to 15 minutes (12, 13). In refractory cases, benzodiazepine preparations (lorazepam, diazepam, midazolam) are used (12, 13). Lidocaine is an effective drug for treating refractory seizures as a second or third-line choice (12, 13). Levetiracetam is a new anticonvulsant drug that has become the drug of choice for treating refractory neonatal seizures, and in some centers, it is also used as a second-line drug before benzodiazepines and lidocaine (13). According to the available data, levetiracetam appears to have few side effects and no interactions, and it is available in intravenous form (13).

Outcome: newborns with seizures have a high risk of death in the neonatal period, ranging from 10 to 35%. Seizures can cause loss of neurons and reduce neurogenesis and dendritic density of the spinal cord (14, 15). Epilepsy is a common outcome in infants with seizures, occurring after a latent period in approximately 25%. Infants with cerebral palsy who survive neonatal seizures are eight times more likely to develop epilepsy (15). Global developmental delay is reported in approximately 40% of children who survived neonatal seizures in a single center (15). In a population-based study of the outcomes of infants with seizures, 20% had an intellectual disability, and 27% had a learning disability (15). Long-term outcome in children with neonatal seizures depends on EEG activity, response to anticonvulsant therapy, and ARGAR score (14). More recently, genetic testing of newborns with seizures is increasingly available, which may allow targeted treatment of newborns with genetic epilepsies (1).

## MATERIAL AND METHODS

This is a clinical, observational, one-year, retrospective, cross-section study. The research included newborns who were hospitalized in the Neonatal Intensive Care and Neonatology department from January 1<sup>st</sup> to December 31<sup>st</sup>, 2021. Out of 598 hospitalized newborns, 43 had seizures and are included in the research. The diagnosis of seizures of the newborns included in the study was made based on a clinical picture. We have analyzed data regarding sex, gestational age, delivery mode, birth weight, and APGAR score.

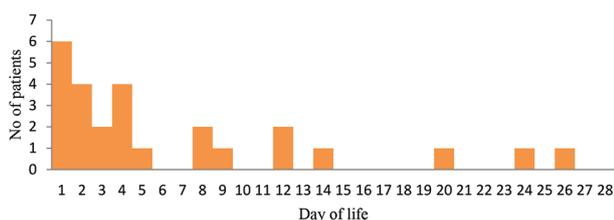
We have also analyzed the etiology and predisposing factors for seizures, the day of life in which seizures were noted, and the characteristics of seizures. We have analyzed laboratory findings (FBC, minerals, blood gases, D-dimer, blood culture), brain US, brain MRI, and EEG.

### Statistics

The data were processed using the Excel program and presented in tables and graphics. Statistical analysis and hypothesis testing were done using IBM SPSS software. The Chi-square test was used for binary variables, t-test was used for continuous variables. Statistics tests were carried out at the 95% significance level.

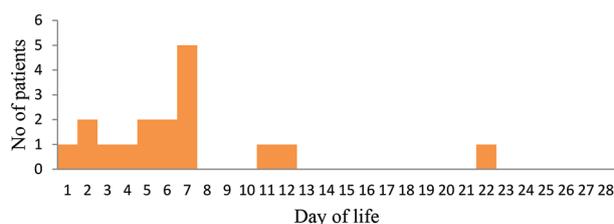
## RESULTS

Out of the total number of hospitalized neonates (598), 43 (7.19%) had seizures. There were 251 preterm infants, of which 17 (6.77%) with convulsive attacks, and 347 term infants, of which 26 (7.49%) with seizures. The increased incidence of seizures in the group of term infants compared to premature infants is not statistically significant.  $\chi^2$  test = 0.1131,  $P = 0.736639$  ( $P > 0.05$ ). Of the total number of newborns with seizures, 18 (41.86%) were female and 25 (58.14%) were male. The increased incidence of seizures in the group of male infants compared to female infants is not statistically significant.  $\chi^2$  test = 0.3436,  $P = 0.557731$  ( $P > 0.05$ ). Six full-term newborns had a seizure on the first day of life, followed by the second and fourth days of life. The mean value of the first day of onset of seizures in term infants is 6.69 days, while the median is four days of life.



**Figure 1.** Time of occurrence of the first seizure in full-term infants

Five premature infants, had seizures on the seventh day of life, followed by the second, fifth, and sixth days of life. The mean value of the first day of onset of seizures in premature infants is 6.7 days, while the median is six days of life. The median of the first day of onset of seizures between the categories of term infants and premature infants is not statistically significant. T-test = 0.0068,  $P = 0.9946$  ( $P > 0.05$ , CI 95% from -4.04 to 4.06)



**Figure 2.** Time of occurrence of the first seizure in premature children

Of the total number of term infants with seizures, nine had HIE, five had some type of intracranial hemorrhage, five had some cerebral malformation, and three had cerebrovascular insult. Ten term infants had some infectious disease. Three infants had an early neonatal infection, two had sepsis and meningitis caused by E. Coli, two had Herpes simplex virus sepsis, and one developed encephalitis. Two infants had meningitis of unknown cause. One newborn had a Cytomegalovirus infection.

Of the total number of premature infants with convulsions, seven had some type of intracranial hemorrhage, six infants had hypoxic-ischemic encephalopathy, while cerebrovascular insult and cerebral malformations were not recorded in premature infants. Of the total number of premature infants, three had some type of infectious disease. Two infants had sepsis and one had meningitis. Of the metabolic disorders, which were recorded in newborns with seizures, we found 10 with hypoglycemia, 24 with acidosis, 14 with hypocalcemia, 7 with hyponatremia, and 5 with hypomagnesemia. Of the total number of cases of hypomagnesemia, four cases were combined with hypocalcemia (80%).

Eight patients had elevated D-dimer values. There were three whose mothers have recently recovered from COVID-19 infection. All of the newborns had some type of thrombosis (sagittal sinus, transverse sinus, and/or the internal carotid artery). Table 1 shows patients with elevated D dimer and their risk factors.

18 patients had an EEG registration performed (41.86%), out of which 11 had normal results (61.11%), and seven infants had epileptic activity recorded on the EEG (38.89%).

The initial treatment for seizures was phenobarbitone in 25 newborns (58%), five (12%) got unspecified anticonvulsants, and one (2%) received diazepam during transport in an ambulance. 12 infants received no drugs. Out of 25 newborns who received phenobarbitone, in 21 cases (84%) seizures have stopped. The other four had additional drugs: midazolam, levetiracetam, and pyridoxine. One infant received three different anticonvulsive drugs.

Out of 43 infants with seizures, 16 (37.21%) were cured without repeated attacks and therapy. In 11

**Table 1.** Patients with elevated D dimer and their risk factors

Patient	Mother's diseases	Infant's diseases
1	Hyperthyroidism, elevated blood pressure, recovered from COVID 19 infection	Internal carotid artery thrombosis, cystic leukomalacia
2	Thrombophilia, recovered from COVID 19 infection	Transverse sinus thrombosis, thrombophilia, thalamostriate vasculopathy
3	No data	E. coli sepsis, meningitis
4	Seizures since the age of 14	No proven diseases
5	Elevated blood pressure, recovered from COVID 19 infection	Sagittal and transverse sinus thrombosis
6	No data	Sagittal sinus thrombosis
7	No data	Thalamostriate vasculopathy, an anatomical variation of the internal carotid artery
8	No proven diseases	Meningitis

(25.58%) newborns, therapy was continued with some of the anticonvulsants to keep the seizures under control. Death was recorded in 16 (37.21%) newborns. Of the total number of deaths in children with convulsions, there were 13 premature and three term children. RR = 0.62 (term infants), RR = 1.61 (preterm infants). The increased mortality of premature newborns with seizures compared to full-term newborns is statistically significant.  $\chi^2 = 59.4099$ ,  $P < 0.00001$ , ( $P < 0.05$ ).

## DISCUSSION

According to research conducted by Carlotta Spagnoli, Raffaele Falsaperla, and others, in 2018, neonatal seizures occur in up to 1.5-3.5/1000 full-term infants and 10-130/1000 premature infants (16). In our research, the prevalence of attacks among premature infants was 6.77%, and among term children 7.49%. A common problem is the failure to recognize subtle seizures, which are more prevalent in premature infants, and subclinical seizures, which occur in both full-term and premature infants. In our study, of the total number of newborns with convulsive attacks, there were more male newborns (58.14%).

The onset of seizures in premature infants tends to occur later than in term infants (16). It is believed that the difference in the onset of seizures in premature and term infants is a consequence of the different etiology of seizures (16). In our research, it was found that the median of the first day of onset of seizures in full-term infants is on the fourth day, while in premature infants, it is on the sixth day of life. Our sample, although small, is consistent with the results of larger studies.

Research by C. Glass, A. Shellaas, and others, published in 2017, included 611 infants with seizures (17). Hypoxic-ischemic encephalopathy was described as the most common etiological cause of seizures among

premature and full-term infants, and intracranial bleeding in premature newborns (17). Cerebrovascular insults were more often diagnosed in term infants, while intracranial infections were more common in premature infants (17). In our work, it was noted that the largest number of term newborns had hypoxic-ischemic encephalopathy, followed by intracranial bleeding and then cerebral malformations. Cerebrovascular insult was recorded in three cases in term infants. Some infants had more than one etiological factor.

In the Iraqi study from 2018, 203 newborns with seizures were included, of which 28 had hypocalcemia (13.79%) (18). In our study, we had hypocalcemia in 14 newborns, or 32.56%. In a study from 2017 that included 150 newborns with recorded seizures (19) 5.3% of newborns with hypomagnesemia were discovered. 33 87% of hypomagnesemia cases were associated with hypocalcemia, which implies a mutual connection in the pathophysiology of these disorders. In our sample, 11.63% of cases of hypomagnesemia were recorded, of which 80% were associated with hypocalcemia. Studies such as the one by K. Williams and A. Singh found 16.81% of children with seizures to have a reduced pH value (20). The same study concluded that in univariate analysis, acidosis was significantly associated with seizures. We recorded acidosis in 24 infants (55.81%). In the current literature, increasingly frequent reports of neonatal seizures have been observed in newborns of mothers who had a COVID-19 infection during pregnancy. One of the reports published in 2022 presents a case of central venous sinus thrombosis of a newborn whose mother had a COVID-19 infection in the first month of pregnancy (21). Also, Parul Jain, Anup Thakur et al. published a 2020 case report of a newborn, COVID 19 of a positive mother, who was diagnosed with acidosis and thrombocytopenia at birth, associated with intracranial

bleeding (22). Manas Kumar Nayaka, Santosh Kumar Panda et al. in study 2021 included 162 COVID 19 positive mothers (23). Nine infants of positive mothers developed infection and eight had neonatal seizures. We recorded three cases of mothers who suffered from COVID-19 during pregnancy and whose newborns had seizures. Some type of intracranial thrombotic process (arteriae carotis internae thrombosis, sinus transversus thrombosis, and sinus sagittalis et transversus thrombosis) was detected by the MRI technique in the mentioned newborns. The presented cases could point to a connection between the mother's COVID-19 infection and an increased predisposition to the occurrence of thrombotic incidents in newborns, which should be the subject of further research.

In 2007, Ajay Kumar, Ashish Gupta, and Bibek Talukdar published a study in which 90 infants with a clinical picture of seizures were included within one year (24). Of the 60 EEG recordings performed, only one-third had an abnormal finding. In our work, we noted that 41.86% of children with realized EEG registration, 38.89% had an abnormal EEG finding.

In 2019, E. Baudou, C. Rakovi, and others published a study based on the follow-up of 319 newborns with neonatal seizures (6). 243 newborns received anticonvulsant therapy, of which one-third received monotherapy and two-thirds polytherapy (6). Phenobarbitone was prescribed in 199 cases (82%), diazepam in 111 (46%), and phenytoin in 79 cases (32%). 86% of infants primarily treated with diazepam needed second-line therapy, which in most cases was phenobarbitone. In maintenance therapy, valproic acid 50%, carbamazepine 11%, levetiracetam 7%, phenobarbitone 2%, and 2% others. In 28% of cases, no maintenance therapy was prescribed. Another study published in 2020 by researchers Cynthia Sharpe, Gail E. Reiner, and others, was based on a randomized cohort study of infants with seizures, who were randomly divided into two groups (25). In one group, the infants received phenobarbitone therapy while in the second group received levetiracetam. 80% of infants randomized to phenobarbitone had seizures stopped within 24 hours, compared to 28% of infants randomized to levetiracetam. By increasing the dose of levetiracetam from 40 to 60 mg/kg, a 7.5% improvement in effectiveness was achieved. In our study, 25 infants received phenobarbitone in the initial treatment (58%). For five children we do not have exact information on which drug it was, one newborn received diazepam as an initial treatment, to which he responded positively. 12 infants were without initial treatment (28%). Of the total number of infants who received phenobarbitone in the initial treatment, 21 infants responded successfully (84%). Of the cases in which there was no suc-

cess in stopping the attack with phenobarbitone, in one case it was stopped with midazolam, in another with levetiracetam, and in two cases pyridoxine was used which stopped the attack in one newborn, while it did not in the other. The infant who did not respond to either phenobarbitone or pyridoxine therapy, was treated with levetiracetam, also without success.

The conclusion of a systematic review (26) comparing the efficacy and safety of levetiracetam and phenobarbitone in the treatment of neonatal seizures is that levetiracetam shows promising results, with better efficacy in seizure control and safety, and with fewer side effects than phenobarbitone, which is currently used as a first-line drug in neonatal seizures. The researchers state that long-term follow-up studies are needed to determine the neuroprotective effect of levetiracetam on neonatal brain development, leading to a better neurodevelopmental outcome compared to phenobarbitone. In a study published by Renée A. Shellhaas, Courtney J. Wusthoff et al. in 2021, 282 infants with a history of neonatal seizures were followed (27). In this large study of infants who survived neonatal seizures, the majority (87%) did not develop post-neonatal epilepsy before 24 months. Infants who developed epilepsy had up to three times the risk of developing a neurodevelopmental disorder. Another study on the neurodevelopment of infants after neonatal seizures was published in 2011 by researchers Jarred Garfinkle and Michael I. Shevella, who observed 120 newborns (28). Of the total number of newborns (120), 45% did not have any neurodevelopmental disorders, 31% had cerebral palsy, 43% had developmental delays, and 32% had epilepsy. A similar study was conducted in 2015 at the Sarajevo Pediatric Clinic, where the neurodevelopment of 100 infants with neonatal seizures was monitored (29). 62.33% of the children showed a developmental discrepancy. This research concludes that neonatal seizures have a strong predictive association with short-term and long-term causes of mortality and morbidity. According to a 2020 study by Monica E. Lemmon, and Sonia L. Bonifacio et al., among 611 infants followed with seizures, 90 infants (15%) died during hospitalization (30). The most common etiology of fatal seizures in infants was: hypoxemic-ischemic encephalopathy. Research from 2016 (31) shows mortality in the first year of life, of infants with seizures in the neonatal period, of 23%. Death was more common in premature infants (33.3%) than in term infants (17.9%). Mortality was higher among male full-term infants than among female full-term infants. In our work, the mortality of children with recorded convulsions was 37.2% (72.9% of which were premature) of which a fatal outcome was recorded, had some type of intracranial hemorrhage, then hypoxemic-ischemic encephalopathy, and cerebral malformations.

## CONCLUSIONS

In our study, we observed a higher prevalence of seizures in term than in premature infants, which is probably a consequence of not recognizing subtle and subclinical seizures and a small sample, but also a larger total number of hospitalized term infants. Seizures in term infants occur earlier than in premature infants. The most common etiology of seizures in term infants are infections, hypoxemic-ischemic encephalopathy, intracranial hemorrhage, cerebral malformations, and cerebrovascular insult. In premature infants, these are hypoxemic-ischemic encephalopathy, intracranial bleeding, and infections. Among the metabolic disorders in patients with convulsions, acidosis, hypoglycemia, hypocalcemia, hyponatremia, and hypomagnesemia (alone and in combination with hypocalcemia) were found to be the most common. The occurrence of thrombosis (art. carotis interna, sinus sagittalis, sinus transversus), followed by seizures, in newborns whose mothers suffered from the COVID 19 infection, due to the greater number of recorded cases, should be the subject of further research. In the initial treatment of neonatal convulsions,

phenobarbitone is most often used, which has proven to be extremely successful in the majority of cases. According to many studies, levetiracetam gives promising results, with better efficacy in seizure control and safety, fewer side effects, and better neurodevelopmental outcomes compared to phenobarbitone. Increased mortality of infants with neonatal seizures was observed, compared to the total number of recorded deaths, especially in the group of premature infants (76.47%). The highest mortality rate is for newborns who had some type of intracranial bleeding as an etiological cause.

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## Sažetak

### NEONATALNE KONVULZIJE: ETIOLOGIJA, TRETMAN I PROGNOZA

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**Uvod:** Konvulzije su jedna od najčešćih patologija u novorođenčadi. Njihova učestalost je 1,5-3,5/1000 za terminsku dojenčad i 10-130/1000 za nedonošćad. Najčešći uzroci konvulzija u terminske dojenčadi su hipoksično-ishemijska encefalopatija (HIE), cerebrovaskularni inzult (CVI), cerebralne malformacije (CM) i metabolički poremećaji, a u nedonošćadi: intraventrikularno krvarenje (IVH), periventrikularna leukomalacija (PVL) i infekcije. Kliničke karakteristike su raznolike i suptilne, a česti su subklinički oblici. Lek prvog izbora je fenobarbiton. Novorođenčad s konvulzijama sklonija su razvoju neuroloških poremećaja poput epilepsije i cerebralne paralize.

**Metode:** Ovo je kliničko, opservacijsko istraživanje, jednogodišnja, retrospektivna, studija preseka, sprovedena na Odeljenju za neonatalnu intenzivnu negu i neonatologiju Klinike za pedijatriju Kliničkog centra Univerziteta u Sarajevu. Istraživanje je obuhvatilo 43 novorođenčadi koja su zadovoljila kriterijume uključivanja.

**Rezultati:** Otkrili smo da je 7,19% hospitalizovane novorođenčadi imalo konvulzije. Velik broj napada zabeležen je u grupi terminske novorođenčadi s ranijim po-

četkom konvulzija. Najčešći etiološki uzroci bili su: HIE, IVH, infekcije i CM. Česta je bila pojava metaboličkih poremećaja poput acidoze, poremećaja šećera u krvi i minerala (Ca, K, Na i Mg). Medijan prvog dana početka konvulzija u donošene dece je četvrti dan, dok je u nedonošćadi šesti dan života. Fenobarbiton se uglavnom koristio za zaustavljanje konvulzija, s velikim uspehom. Ukupna smrtnost u dece s konvulzijama bila je 37,21%.

**Zaključak:** Kod novorođenčadi su česte konvulzije koje, zavisno od etiološkog uzroka, povećavaju mortalitet, naročito kod nedonošćadi. Konvulzije se u donošene dece javljaju ranije nego u nedonošćadi. Najčešća etiologija konvulzija u donošene dece su: infekcije, hipoksemično-ishemijska encefalopatija, intrakranijalno krvarenje, cerebralne malformacije i cerebrovaskularni inzult. U nedonošćadi to su: hipoksemično-ishemijska encefalopatija, intrakranijalna krvarenja i infekcije. U početnom lečenju neonatalnih konvulzija najčešće se koristi fenobarbiton, koji se pokazao uspešnim u većini slučajeva.

**Ključne reči:** neonatalne konvulzije, etiologija, lečenje, prognoza, mortalitet.

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