RESEARCH ARTICLE

CYPRUS
JOURNAL OF MEDICAL SCIENCES

DOI: 10.4274/cjms.2023.2022-41
Cyprus J Med Sci 2023;8(6):406-410

Epilepsy After Neonatal Seizures: Etiologies, Clinical and Developmental Outcomes

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Abstract

BACKGROUND/AIMS: The newborn period has the highest risk of seizures and the majority of these seizures are symptomatic. Children with neonatal seizures have a higher risk of epilepsy. The aim of the present study was to identify etiological factors, clinical characteristics, and seizure control in children with epilepsy with a history of neonatal seizures.

MATERIALS AND METHODS: Children who were diagnosed with epilepsy between January, 2014 and January, 2021 were evaluated. Among 220 epileptic children, the ones who had a history of newborn seizures and a follow-up of more than 5 years were enrolled in this study.

RESULTS: Among the 41 patients, 14 (34.1%) were girls and 27 (65.9%) were boys. The mean age at the diagnosis of epilepsy was 3.2 months. Etiological factors were demonstrated in 26 (63.4%) of the patients. Hypoxic-ischemic encephalopathy was the main cause and it was reported in 13 (31.7%) patients. Twenty-five (61%) patients had both mental and motor retardation, whereas 1 (2.4%) patient only had mental retardation. Abnormal findings on magnetic resonance imaging (MRI) were documented in 27 (65.9%) of the patients. A statistically significant association was found among mental motor retardation and the presence of abnormality on MRI scans. Seizures were controlled in 27 (65.9%) of the patients, whereas 14 (34.1%) of the patients had refractory seizures.

CONCLUSION: Epileptic children with previous neonatal-onset seizures had a higher incidence of mental motor retardation and refractory epilepsy. The onset age of epilepsy was during early infancy. Abnormal findings on MRI scans were warning signs for poor prognosis and related to mental and motor retardation, but not related to seizure control.

Keywords: Epilepsy, newborn seizure, developmental delay, magnetic resonance imaging, seizure control

INTRODUCTION

The neonatal period is the period of life in which the incidence of seizures is the highest. Incidence was documented in 2.6 out of 1,000 live births, whereas it was documented in 8.6% of infants who were hospitalized in newborn intensive care units.[1,2] The majority of newborn seizures are acute symptomatic seizures. Acute symptomatic seizures are seizures which are triggered by precipitating factors such as hypoglycaemia, asphyxia, or trauma. Hypoxic ischemic encephalopathy (HIE), metabolic disturbances such as hypoglycaemia, hypocalcaemia, hypomagnesemia, intracranial haemorrhage (ICH), ischemic stroke, and central nervous system infections are the main underlying etiologies.[3,4]

In addition, neonatal seizures may have a poor prognostic effect on brain development, which may result in developmental delay, cognitive disorders, epilepsy or cerebral palsy.[5-8]

*Study performed in Near East University and Dr. Suat Günsel University in North Cyprus.

To cite this article: Şanlıdağ B, Dirik MA, Dirik E. Epilepsy After Neonatal Seizures: Etiologies, Clinical and Developmental Outcomes. Cyprus J Med Sci 2023;8(6):406-410

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Received: 16.09.2022
Accepted: 28.02.2023

Epilepsy was reported at rates of up to 56% in different studies of children who had neonatal seizures. The risky period for the emergence of epilepsy after neonatal period seizures was demonstrated to be within the first year of life.[9-15]

The risk factors for future epilepsy in cases with symptomatic seizures in neonates were revealed to be premature birth, low scores of APGAR, abnormal neurological examination, low blood pH levels within the first day of life, abnormalities on background activity within electroencephalogram (EEG) records, status epilepticus and the presence of brain injury.[15] Children with brain insult have a high risk of epilepsy.[7,11] Thus, neuroimaging is an important diagnostic tool for the etiological workup of children with epilepsy. International guidelines for neuroimaging recommend magnetic resonance imaging (MRI) for all children with epilepsy before the age of 2 years.[16]

Children with seizures starting before the age of 2 years demonstrated poor seizure control, poor cognitive and behavioural outcomes in addition to lower rates of being seizure-free in follow-up. Symptomatic causes of epilepsy are more frequent within that group of patients.[17-20]

The aim of the present study was to identify the clinical characteristics and seizure control of children diagnosed with epilepsy with a history of newborn onset seizures.

MATERIALS AND METHODS

This study was designed as a retrospective study. Among 220 patients between 0-18 years old who were examined in the department of child neurology from January, 2014 to January, 2021, those diagnosed with epilepsy with a record of newborn onset seizures were enrolled in this study. Children with follow-up periods of more than 5 years were evaluated. This study was approved by the Ethics Committee of Near East University (approval number: YDU/2018/55-524, date: 22.02.2018). No informed consent was taken as this study was designed as a retrospective study. The clinical data of the patients, neonatal EEG records, the MRI results were obtained from the patients' files and/or hospital databases.

Epilepsy is defines as ≥2 untriggered seizures 24 hours apart or a single unprovoked seizure with a high-risk of recurrence such as seizure with an underlying structural abnormality in addition to epileptiform EEG.[21]

Neurodevelopmental outcomes were based on neurological examination and/or Denver tests.

Interictal EEGs records were performed according to the international 10-20 system, using the NicoletOne device by positioning the electrodes on the scalp. Silver-silver chloride electrodes were used and conductive paste was used to fill the space between the electrodes and the skin. A 16-channel EEG was taken. Low-pass filter, high-pass filter, and notch filter (70 Hz, 1 Hz, and 50 Hz respectively) at a rate of 30 mm/second were applied. Records of a minimum of 30 minutes were taken in sleep and awake states. Subsequently, the EEG records were evaluated by a paediatric neurologist. The diagnosis of epilepsy was made by the existence of two or more unprovoked seizures and the findings of EEG records.

Forty-one patients underwent an MRI scan. MRI was performed using a 1.5 Tesla and 3 Tesla Siemens scanner with a specialized paediatric protocol for epilepsy.

The protocol consisted of (a) sagittal spin-echo T1-weighted, (b) axial fast spin-echo T2 weighted, (c) fast multiplanar coronal oblique inversion recovery, (d) fast fluid-attenuated coronal oblique inversion recovery, (e) axial diffusion (single shot, echoplanar spin echo), b=1,000 multi directions, and (f) three-dimensional axial spoiled gradient echo. MRIs were initially performed without the use of contrast material. In cases with suspicious findings during the scan, gadolinium was used to characterize the lesion better.

Statistical Analysis

For analysis, the Statistical Package for Social Sciences (SPSS) (version 17.0; IBM, Armonk, NY) was used. The used tests were the chi-squared test, Fisher's exact test, and descriptive statistics. A p-value less than 0.05 was considered to be statistically significant.

RESULTS

Forty-one patients were enrolled in this study. Fourteen (34.1%) were girls and 27 (65.9%) were boys. The mean age at diagnosis with epilepsy was 3.2 months.

Parental consanguinity was present in 6 patients (14.6%). Familial epilepsy was detected in 4 patients (9.8%), of whom 2 of the patients' mothers had epilepsy and the other two had epilepsy in relatives other than their parents or siblings.

Etiological factors were documented in 26 (63.4%) patients. Etiological factors were categorized as brain insult (hypoxic-ischemic encephalopathy, haemorrhage, or stroke), metabolic disorder, syndrome, or others, as shown in Table 1.

No relation between seizure type and etiological factors was revealed.

Neuroimaging (MRI) revealed pathological findings in 27 (65.9%) of the patients and 14 (34.1%) of the patients had normal MRI. The MRI findings are shown in Table 2.

Twenty-five (61%) patients had both mental and motor retardation and 1 (2.4%) patient had mental retardation without motor retardation.

The presence of structural abnormality on MRI was shown to have a statistically significant relation with mental-motor retardation (p=0.003).

The mean age at the initiation of treatment was 3.2 months.

Table 1. Identified etiological factors in patients

Etiological factor	Number of patients	% of patients
Brain insult - Hypoxic-ischemic encephalopathy; - (term-born /preterm born) - haemorrhage-stroke	18 13 8/5 5	43.9
Metabolic disorder -Canavan disease -Krabbe disease -Methylmalonic acidemia	3	7.3
Syndrome	2	4.9
Others (cardiopathy, external hydrocephaly, pachygyria)	3	7.3
Total	26	63.4

Among the patients, 26 (63.4%) of them were using one antiepileptic treatment, 12 (29.3%) of them were using 2, and 3 (7.3%) of them were using 3 or more antiepileptic treatments.

The mean follow-up period was 67.2 months.

When the patients were evaluated in order to determine if they had been seizure-free for the previous 1 year of follow-up, it was found that 27 (65.9%) of the patients had had no seizures, whereas 14 (34.1%) of the patients had experienced seizures. During the follow up, antiepileptic treatment was stopped in 7 (17.1%) patients. This data is shown in Figure 1.

No relations reaching statistical significance were documented between MRI findings and the age at the onset of epilepsy, seizure control, or antiepileptic treatment ($p>0.05$).

No correlation between refractory seizures and seizure etiology was noted.

DISCUSSION

Seizures have the highest prevalence during the neonatal period.[1,2] Post-neonatal epilepsy has been reported at rates as high as 56% in different studies.[9-12] Etiology is an important predictor for future epilepsy.[12]

Etiological factors were documented in 26 (63.4%) of the patients within this study group. Among them, the majority had a brain insult (22%). Within the group of patients with a brain insult, hypoxia was the leading cause, which was documented in 8 (19.5%) term and 5 (12.2%) premature newborn. The second most common etiology was ICH and stroke. Similarly, in a study evaluating the etiological profiles of seizures in term neonates, perinatal asphyxia was the leading etiological factor, and secondly, perinatal arterial ischemic strokes were observed.[12] HIE also constitutes approximately 40% of all neonatal seizures.[22,23] Within term and late premature infants, the most commonly seen reason for seizures are ischemic, ICH, metabolic and electrolyte disturbances, and infectious causes.[22,24,25] More specifically, HIE increases the risk of newborn seizures in term neonates three-fold in comparison to premature neonates.[2] Within that study, the number of epileptic children who were born at term was higher than those who were born preterm. Additionally, the presence of seizures in cases of HIE has been suggested to be a sign of a more severe outcome.[26] In other studies, cerebral palsy was reported to be a very important risk factor for future epilepsy with an 8-fold increased risk.[7,11,27] The most commonly seen neurological problems in children after neonatal seizures are developmental delay, epilepsy, and cerebral palsy.[5-8] Supporting those findings in the literature, in this study, 25 (61%) of the children had mental motor retardation in which 13 (31.7%) of them were due to HIE.

Table 2. MRI findings

MRI findings	Number	%
Normal	14	34.1
Term HIE	8	19.5
Periventricular leukomalacia	5	12.2
Haemorrhage-stroke	5	12.2
Developmental brain abnormalities (holoprosencephaly, meningomyelocele, corpus callosum agenesis, cortical dysplasia)	5	12.2
Suggestive of metabolic disorder	3	7.3
Increased signal intensity	1	2.4
Total	41	100

MRI: Magnetic resonance imaging, HIE: Hypoxic ischemic encephalopathy.

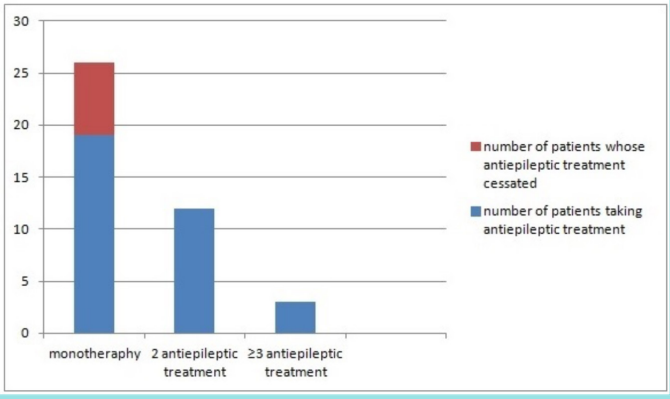

Figure 1. Treatment in follow-up.

In another study, pathological findings in neonatal cerebral ultrasound and familial epilepsy were reported as independent risk factors for future epilepsy, highlighting the genetic and prenatal etiology of seizures.[28] Other than brain injuries, newborn period seizures were also reported to cause an increase in the risk of epilepsy.[13] In contrast to our study, developmental brain abnormalities were the leading cause of epilepsy with a rate of 21% in an infancy onset epilepsy cohort. It has been documented that the incidence of epilepsy is higher in underdeveloped countries. This is postulated to be related to higher cases of brain insult, CNS infections, and trauma-related cases in underdeveloped countries.[29,30]

In this study population, pathological MRI findings were present in 65.9% of the patients. Although there is no similar study to compare with, a population-based study evaluating newly diagnosed epileptic infants reported the etiological relevance of abnormality in 51% of patients. An MRI abnormality rate of 57% was documented in cases younger than 2 years old in a hospital-based cohort.[31]

Among the 41 patients in this study, 25 (60.9%) among them had both mental and motor retardation and 1 (2.4%) patient had only mental retardation without motor retardation. Studies have reported global developmental delay in 30-50% of children after neonatal seizures.[5,6,32] Various risk factors had been linked to poor prognosis after neonatal seizures including low birth weight, prematurity, severe HIE, low APGAR scores, high-grade intraventricular haemorrhage, persistent abnormal background activity on EEG records, seizures starting before 24 hours and after 72 hours of life, status epilepticus, CNS infections and brain insult shown by MRI.[4,15,22,33,34] Despite knowledge of certain indicators of poor prognosis, the prediction of individual outcomes is still challenging in cases with acute symptomatic seizures within the newborn period.[19] Additionally, regarding cases of epilepsy in the infantile period, high rates of patients were reported to have developmental and cognitive impairments in long-term follow-up.[17-19]

Abnormality on MRI was found to be significantly related to the presence of mental-motor retardation in this study. However, no correlation was documented between seizure control in the last year

of follow-up and MRI findings. Pisani and Spagnoli[26] reported that symptomatic epilepsy groups of patients had worse seizure control in addition to higher rates of developmental impairment. In another study supporting our findings, MRIs without significant lesions were found to be related to a low risk of neurodevelopmental impairment and recurrent seizures. This highlights the importance of MRI imaging not only for the demonstration of underlying etiological disorders, but also for the estimation of long-term outcomes.[35,36]

The mean age at the time of diagnosis of epilepsy and the onset of antiepileptic drugs was 3.2 months in our study group of patients. During the first year of life, there is an increased risk for the emergence of post-neonatal epilepsy.[13,14] Similarly, it has been reported that symptomatic reasons for epilepsy are more common during the infancy period of life.[20]

Within this study, 26 (63.4%) of the patients were using one antiepileptic drug regimen, 12 (29.3%) of them were using 2 drugs and 3 patients (7.3%) were using 3 or more antiepileptic drugs. Twenty-seven (65.9%) of the patients had had no seizures during the previous 1-year period, whereas 14 (34.1%) of the patients had experienced ongoing seizures. A higher rate of seizures refractory to initial medication during the newborn period was documented by Glass et al.[22] in another study in patients with etiological factors of HIE, stroke, and ICH. Children with seizures starting before the age of 2 years were also reported to have poor seizure control.[17,18] No statistically significant relation between structural lesions on MRI and treatment response was found in this study.

Study Limitations

The main limitation of the present study was its retrospective manner.

CONCLUSION

In conclusion, epileptic children with neonatal-onset seizures were found to have 63.4% of underlying etiological factors. Although no statistically significant relationship could be demonstrated between seizure control and MRI findings, the presence of structural abnormalities on MRI was found to have a statistically significant correlation with mental-motor developmental delays. The incidence of refractory seizures and mental-motor retardation is high in epileptic children with neonatal seizures. Therefore, it can be postulated that MRI findings can be a warning sign for upcoming developmental delays. In this way, MRI results may guide the early initiation of rehabilitation which can decrease long-term adverse effects and improve outcomes.

MAIN POINTS

- Epileptic children with neonatal-onset seizures were found to have 63.4% of underlying etiological factors.
- The presence of structural abnormalities on MRI was found to correlate with mental-motor retardation, but was not related to seizure control.
- The incidence of refractory seizures and mental-motor retardation was high in epileptic children with neonatal onset seizures.
- Early MRI imaging is important in children with neonatal seizures, not only for the etiological factors, but also to estimate possible developmental delays and improve outcomes.

ETHICS

Ethics Committee Approval: This study was approved by the Ethics Committee of Near East University (approval number: YDU/2018/55-524, date: 22/02/2018).

Informed Consent: No informed consent was taken as this study was designed as a retrospective study.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Concept: B.Ş., M.A.D., E.D., Design: B.Ş., M.A.D., E.D., Data Collection and/or Processing: B.Ş., M.A.D., E.D., Analysis and/or Interpretation: B.Ş., M.A.D., E.D., Literature Search: B.Ş., M.A.D., E.D., Writing: B.Ş., M.A.D., E.D.

DISCLOSURES

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study had received no financial support.

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