Postneonatal Epilepsy and Psychomotor Developmental Retardation Risk Factors in Term Neonatal Convulsions Without Hypoxic Ischemic Encephalopathy

Doğumsal Hipoksik İskemik Ensefalopatiye Bağlı Olmayan Term Yenidoğan Konvülziyonlarında Psikomotor Gerilik ve Epilepsi Gelişim Risk Faktörleri

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ABSTRACT

Objective: Neonatal convulsions may be an early sign of brain injury and the presence of convulsions in the neonatal period has been associated with long-term sequelaes such as mental retardation, postnatal epilepsy and death. We aimed to determine associations of etiological factors with neurodevelopment and postneonatal epilepsy and evaluate the risk factors in newborns with neonatal convulsions that were not related to hypoxic-ischemic encephalopathy.

Material and Methods: This study included full-term infants who were born between January 2010 and December 2014 and had neonatal convulsion history, had no history of hypoxic-ischemic encephalopathy and were followed for at least 1 year at our neurology clinic.

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Results: Forty-nine patients were included to the study. Among the identified etiologies on first clinical visit, hypoglycemia was the most common cause which was presented in 11 (40.74%; 11/27 patients) patients. During follow-up, 22.4% (n=11) of patients developed postneonatal epilepsy. In 4 of 7 patients with abnormal Bayley II test results, epilepsy developed in the follow-up. The risk for development of postneonatal epilepsy was significantly associated with abnormal neurological findings, such as cerebral palsy or significant delays in developmental stages; being not benefited from acute treatment and follow-up abnormal EEG findings of the patients.

Conclusion: Hypoglycemia should be primarily investigated and treated in term neonatal seizures without hypoxia. Abnormal neurological findings, being not benefited from the acute treatment and follow-up EEG findings were associated with developing epilepsy. In the literature, most of the studies were limited due to short follow-up periods. More information about prognostic factors in neonatal convulsions and the occurrence of postneonatal epilepsy is needed.

Key Words: Neonatal seizures, Hypoglycemia in newborn seizures, Postneonatal epilepsy

ÖZ

Amaç: Yenidoğan konvulziyonları, yenidoğan döneminde akut nörolojik hastalıkların en yaygın semptomlarından biridir. Hastalarda ölüm, mental retardasyon ve postneonatal epilepsi riskini arttırdığı bilinmektedir. Bu çalışmada sebebi doğumsal hipoksik iskemik ensefalopati olmayan ve hastanemizde yenidoğan konvulziyonu sebebiyle takip edilmiş hastalarda etyolojik faktörler ile nörogelişim ve epilepsi ilişkisi ve risk faktörlerinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: Bu çalışmaya hastanemiz nöroloji polikliniğinde takipli, Ocak 2010 - Aralık 2014 tarihleri arasında miadında doğan, doğumsal hipoksik iskemik ensefalopati öyküsü olmayıp, yenidoğan döneminde nöbet öyküsü olan, en az 1 yıl takibimizde kalan hastalar dahil edildi.

Bulgular: Çalışmaya 49 hasta dahil edildi. İlk başvuru sırasında saptanabilen en sık etyolojik faktör, 11 (%40.74) hastada saptanan hipoglisemiydi. İzlemde hastaların %22.4'ünde (n=11) postneonatal epilepsi geliştiği görüldü. Bayley II testleri anormal saptanan 7 hastanın 4'ünde epilepsi geliştiği belirlendi. Yenidoğan döneminde başlanan tedaviye yanıtın olmaması, anormal nörolojik muayene bulgularının varlığı ve izlemde anormal EEG bulgularının olması, hastalarda postneonatal epilepsi gelişimi için risk faktörleri arasındaydı.

Sonuç: Hipoglisemi, yenidoğan nöbetlerinde saptanabilen ve tedavi edilebilen sebeplerden bir tanesidir. Anormal nörolojik muayene bulguları, başlanan tedaviye alınan yanıtlar ve izlem EEG bulguları epilepsi gelişimi ile ilişkili görüldü. Bu konuda yapılmış olan çalışmaların çoğu, kısa gözlem süreleri sebebiyle sınırlıdır. Yenidoğan konvulziyonları ve postneonatal epilepsi gelişimi açısından daha fazla prognostik faktör belirlemek için daha fazla çalışmaya ihtiyaç vardır.

Anahtar Sözcükler: Yenidoğan konvulziyonları, Hipoglisemi, Postneonatal epilepsi

INTRODUCTION

Neonatal convulsions are one of the most common symptoms of acute neurological disorders in the neonates. While conflicting data existed in the literature on these seizures, that may be an early sign of brain injury and the presence of convulsions in the neonatal period reported that is has been associated with long-term sequelae and death (1, 2).

Population-based studies have shown that the incidence of neonatal seizures is 1.8-3.5 per 1000 live births (3). Moreover, post-neonatal epilepsy following neonatal seizures occurs at a rate varying between 1.8% and 41.3% and has an estimated incidence of 70/100.000 among children and adolescents in Europe (4-6). Studies evaluating in newborns without hypoxic-ischemic encephalopathy are limited. Frequent etiologies that were reported, differ from hypoxic-ischemic encephalopathy include focal hypoxia ischemia, intracranial hemorrhage, cerebral malformation, transient metabolic disturbance, perinatal infection, and inborn errors of metabolism (7). Malmqvist et al reported that, 40 newborns had seizures without hypoxic-ischemic encephalopathy and 9 of them had epilepsy (7).

Neonatal seizures are known to increase the risk of death, mental retardation and postnatal epilepsy in affected patients (8). These comorbidities become more prominent when patients develop epilepsy. The coexistence of mental retardation and cerebral palsy was found in 87% of the patients who had neonatal convulsions and developed epilepsy in the follow-up (9).

Since the etiology of neonatal seizures has a treatable cause and convulsions might impair vital functions and lead to brain injury, it is crucial to recognize the seizure and it should be treated appropriately based on the identified etiology in the neonatal period (10).

In the present study, we aimed to determine associations of etiological factors with neurodevelopment and postneonatal epilepsy and evaluate the risk factors in newborns with neonatal convulsions that were not related to hypoxic-ischemic encephalopathy who were followed at our hospital.

MATERIALS and METHODS

This cross-sectional study included full-term infants who were born between January 2010 and December 2014, had neonatal convulsion history, had no history of hypoxic-ischemic encephalopathy and were followed for at least 1 year at our neurology clinic.

The instutional review board approved the study design and protocols (University of Health Sciences, Dr. Sami Ulus Maternity and Children's Health and Disease Training and Research

Hospital; No:73799008-799). Demographic characteristics, mode of delivery, age at the time of seizure, the type and etiology of seizure, anticonvulsant therapy and duration of treatment, neuroimaging findings, diagnostic laboratory studies, follow-up neurological findings and neuromotor and cognitive development levels (Bayley II) and occurrence of epilepsy during follow-up were retrieved from our hospital's electronic medical records and reviewed retrospectively for all patients.

In order to determine whether the time of seizure is a prognostic factor, four groups were formed based on the age of seizure onset: first 24 hours; 24-48 hours; from 48 hours to 1 week; >1 week. Due to the difficulty of obtaining information on the type of seizure from medical files, seizures were classified as subtle and others.

Patients with having clinical seizures in the postneonatal period or abnormal EEG findings were considered as having postneonatal epilepsy.

Neurological examination findings obtained on the last follow-up of patients were divided into two groups as normal/mild deficit and moderate/severe deficit. Patients with normal/mild neurological deficits were defined as those having mild changes in tonus or deep tendon reflex and minimal delays in developmental stages and patients with moderate/severe neurological deficits were defined as those with established cerebral palsy or significant delays in developmental stages.

Assessments performed using the "Bayley Mental Development Index-II/Bayles Scales of Infant Development" at 9 months of age and later were recorded for patients who were followed at the developmental pediatrics clinic up to at least 1 year of age. Scores lower than 70 (2 standard deviations below the mean) were considered as abnormal.

Electroencephalography (EEG); was performed with using the international 10-20 system for electrode placement that has been modified because of the smaller head size of the babies and relatively low EEG activity were noted in the frontopolar head regions and the widely accepted newborn montage system (9-10 electrodes) with anterior-posterior and transverse montage including central vertex (Cz) was used (11). EEG discharges were recorded as normal, focal or multifocal.

Neuroimaging data from transfontanel ultrasonography (TFUSG), computed tomography (CT) and magnetic resonance imaging (MRI) were reviewed and the results were classified as normal and abnormal. Imaging results showing developmental anomalies of brain, changes related to hypoglycemia and hypoxia, myelination defects and hemorrhage, thrombus and infarct findings associated with cerebrovascular events were considered as abnormal.

Statistical analyses were conducted using the IBM SPSS for Windows, Version 22.0 software package. Numerical variables were summarized as mean ± standard deviation and median [minimum – maximum] values. Categorical variables were expressed as number and percentage. Chi-square test or Fisher's exact test was used to compare categorical variables. McNemar's test was used to check whether there were differences between neonatal EEG and follow-up EEG values. Statistical significance was set at $p<0.05$.

RESULTS

In 49 pediatric patients, who were followed for neonatal convulsions and born at term with no history of hypoxic-ischemic encephalopathy, 35 (71.4%) were male. The mean duration of the follow-up was 19.8 months, with a minimum follow-up of 12 months. Twenty-eight (58.3%) patients were born via normal spontaneous vaginal delivery and 20 (41.7%) were born via Cesarean section. Information on mode of delivery could not be retrieved for only one patient. Patient ages at the seizure onset are shown in Table I.

Examinations at the initial presentation have identified an etiological factor in 27 (55.10%) patients through the laboratory studies. Among the identified etiologies at the initial presentation, hypoglycemia was the most common cause which was presented in 11 (40.74%) patients. Data on etiological factors identified at initial presentation are shown in Table I.

Overall, 36 patients were assessed using TFUSG, 7 patients using CT and 30 patients using brain MRI during follow-up. New etiologies were identified with follow-up magnetic resonance imaging in 4 patients in addition to the aforementioned etiological factors. Hypomyelination in 1 patient, hypoxic-ischemic changes in 1 patient and hemorrhagic sequelae findings in 2 patients were reported in MRI findings. Thus, a precise etiological factor had been identified by all of these diagnostic tests in a total of 31 patients (63.2%).

During the follow-up, 22.4% (n=11) of the patients developed postneonatal epilepsy (Table III). Among these patients, in 4 patients hypoglycemia was the etiological factor identified at presentation. Hyperinsulinemic hypoglycemia was diagnosed in 2 of these 4 hypoglycemic patients at follow-up. A patient with subarachnoid hemorrhage developed epilepsy during follow-up and showed abnormal findings on neurological examination. Also, 1 patient with West syndrome, 1 syndromic patient with holoprosencephaly, 1 patient with hypoxia related to cardiac arrest, 2 patients with hemorrhagic sequelae findings on MRI had postneonatal epilepsy. The etiological factor of one patient couldn't be identified.

One patient with meningoencephalitis and one patient with encephalitis had normal neurological examination findings and did not develop epilepsy during follow-up.

The seizure type distributions of patients were as follows, subtle type in 19 patients (38.8%), and the other types in 29 patients (59.2%). Seizure type information of 1 patient could not be reached.

Table I: Etiological factors identified at initial presentation in the terms of seizure onset age.

Age at the seizure onset	Etiological factors identified at initial presentation	Number of the patients	n:49 (%)
0-24 hours	Hypoglycemia Pyridoxine dependent seizure Sinus vein thrombosis Unknown reason	1 1 1 7	10 (20.4%)
24-48 hours	Hypoglycemia Encephalitis Hypoglycemia and meningoencephalitis Cerebral infarct and sepsis West syndrome Unknown reason	6 1 1 1 1 5	15 (30.6%)
48 hours- 1 week	Hypernatremic dehydration Hypoglycemia Hypoxia related to cardiac arrest Intracranial hemorrhage Holoprosencephaly as a syndromic patient Unknown reason	3 1 1 1 1 4	12 (24.5%)
>1 week	Hypocalcemia Hypoxia following cardiac arrest, kernicterus Hypernatremic dehydration Subarachnoid hemorrhage Unknown reason	2 1 1 1 6	11 (22.4%)
Unknown	Hypoglycemia	1	1 (2%)

Table II: The risk factors of the development of postneonatal epilepsy.

Patients	Epilepsy diagnosis n (%)	p
Moderate/severe deficits present in follow-up neurological examinations	5 (62.5%)	0.009
Being not benefited from acute treatment	6 (100%)	<0.000
Abnormal follow-up EEG findings present	5 (100%)	<0.000

Eight (16.3%) patients were not being given an antiepileptic therapy and 2 (4.1%) patients who were given an antiepileptic therapy were not regularly being given their medications by their parents. Of 39 patients initially being given an antiepileptic treatment, 33 (84.61%) patients were benefited from acute therapy and 6 (15.38%) patients diagnosed with postneonatal epilepsy did not receive any benefit from acute therapy.

EEG was performed in 47 patients in the neonatal period. When EEG findings of the patients were divided into three groups as focal, multifocal and normal, EEG abnormality was found in a total of 22 (46.8%) patients including 18 (38.3%) patients with focal abnormality and 4 (8.5%) patients with multifocal abnormalities. EEG findings were normal in 25 (53.2%) patients.

Examination of the follow-up EEG findings of patients showed that 2 (4.1%) patients did not being performed EEG monitoring during follow-up. A total of 5 (10.6%) patients had EEG abnormalities including 3 (6.4%) patients with focal EEG findings and 2 (4.3%) patients with multifocal EEG findings. Forty two (89.4%) patients had normal EEG results. Epilepsy was present in all of these 5 patients with abnormal follow-up EEG results and epilepsy was absent in 38 (90.48%) out of 42 patients with normal follow-up EEG results (p=0.000).

Bayley II test results were normal in 49% (n=24) and abnormal in 14.3% (n=7) of the patients, and 36.7% (n=18) of the patients were not subjected to Bayley II test. Epilepsy developed in 4 of 7 patients with abnormal test results. In the remaining 3 patients who did not develop epilepsy, had focal EEG abnormalities at presentation however their last EEG data were normal.

Follow-up neurological examination findings showed that normal/mild neurological deficits were present in 41 (83.67%) patients and moderate/severe neurological deficits in 8 (16.32%) patients. The risk of developing epilepsy was significantly associated with neurological findings, being not benefited from acute treatment and abnormal EEG findings of the patients at follow-up. The characteristics of patients associated with the increased risk factors of developing epilepsy are shown in Table II.

Patient characteristics including gender (p:0.254), age at the seizure onset (p:0.355), type of the seizure (p:0.732),

Table III: The features of the patients developing postneonatal epilepsy.

Patient	Gender	Mode of delivery	Ages at the seizure onset	Etiology	EEG findings in neonatal period	EEG findings in follow-up	Bayley II results	Follow-up neurological examination
1	F	VD	48 hours-1 week	with holoprosencephaly as a syndromic patient	focal	focal	abnormal	moderate/severe neurological deficits
2	F	CS	48 hours-1 week	hemorrhagic sequelae findings in kranial MRI	focal	normal	abnormal	moderate/severe neurological deficits
3	F	CS	unknown	hypoglycemia	focal	multifocal	unknown	moderate/severe neurological deficits
4	M	CS	24-48 hours	hypoglycemia	normal	normal	normal	normal/mild neurological deficits
5	M	CS	24-48 hours	hemorrhagic sequelae findings in kranial MRI	focal	normal	normal	moderate/severe neurological deficits
6	M	CS	48 hours-1 week	hypoglycemia	focal	focal	abnormal	normal/mild neurological deficits
7	M	CS	48 hours-1 week	hypoxia related to cardiac arrest	focal	normal	normal	moderate/severe neurological deficits
8	F	CS	0-24 hours	unknown	normal	normal	normal	normal/mild neurological deficits
9	M	VD	24-48 hours	hypoglycemia	normal	normal	normal	normal/mild neurological deficits
10	F	VD	24-48 hours	west syndrome	multifocal	focal	normal	normal/mild neurological deficits
11	M	VD	>1 week	subarachnoid hemorrhage	multifocal	multifocal	abnormal	normal/mild neurological deficits

***F:** Female; **M:** Male; **VD:**Vaginal delivery; **CS:**Cesarean section*

neuroimaging findings (p:0.256) and Bayley II test results (p:0.17) were not significantly associated with the development of epilepsy.

A statistically significant association was found between neonatal EEG findings and EEG findings during later follow-up (p=0.000). In addition, follow-up EEG findings were normal in 100% of the patients with normal neonatal EEG findings but 77.3% (n=17) of the patients with focal/multifocal abnormalities had normal follow-up EEG results.

Neonatal EEG findings were significantly associated with final neurological examination findings (p=0.040). Among 25 patients with normal EEG findings, 24 (96%) patients had normal and mild deficits on neurological examination.

A significant association was observed between final neurological examination findings and MRI findings of the patients. Among patients with normal MRI findings, 88.2% had normal and mild deficits on neurological examination (p=0.049).

DISCUSSION

In this study, 49 pediatric patients were included. The most common cause of neonatal convulsions was hypoglycemia which occurred in 11 patients. Epilepsy did not develop in 77.6% of the patients and the risk of developing epilepsy was significantly associated with neurological findings, not being benefited from acute treatment and abnormal EEG findings at follow-up.

Newborns suffering convulsions in the first day or after the third day of life were reported to have poorer outcomes than patients developing convulsions in the second or third days of life (12). In our study, 20.4% (n=11) of the patients suffered a seizure in the first 0-24 hours of life, 30.6% (n=15) of the patients within a period of 24-48 hours after birth, 24.5% (n=12) within 48 hours and up to 1 week, and 22.4% (n=11) of the patients after the first week of life. Time of the seizure onset was not significantly associated with the risk of developing epilepsy and final neurological examination findings.

In the current study, no significant association was found between the type of seizure and epilepsy and this is compatible with the literature that did not show an association between the type of seizure and prognosis of patients (13,14). However, Garfinkle and Shevell found a significant association between the seizure type and neurodevelopmental outcome. They observed poor prognosis in 71% of the patients with a subtle, multifocal clonic, tonic or myoclonic seizure but only 23% of the patients had focal clonic seizures (12).

Several studies have demonstrated that seizure etiology is the major factor in determining the prognosis (13,15-18). In our study, among the identifiable etiologies, the most common cause of the seizures was hypoglycemia (n=11 patients) and postneonatal epilepsy developed in 4 of these patients.

One patient with meningoencephalitis and one patient with encephalitis had normal follow-up neurological examinations and did not develop epilepsy. A patient with subarachnoid hemorrhage developed epilepsy during follow-up and showed abnormal findings on neurological examination.

The risk of developing postneonatal epilepsy (68.5%) (about 3/4 of the patients) was higher in the first year of life and the remaining one-fourth of the cases occurred during in the first 5 years of life (19). Short follow-up period in our study as well as in many other studies precluded the ability to observe the occurrence of epilepsy and to examine the effects of neonatal convulsions on the developing brain in childhood and adolescence, which represents a limitation. The mean duration of follow-up was 19.8 months for our patients.

The prevalence of epilepsy following neonatal seizures was ranged between 16-56% and the rates vary depending on the chosen criteria and the duration of follow-up (20). In a meta-analysis including 44 studies (4 population-based and 40 hospital-based studies) between 1954-2013 showed that among 4538 infants with neonatal convulsion, 17.9% developed postneonatal epilepsy later on (19). Data were also reported separately for preterm infants and term infants with a postneonatal epilepsy prevalence of 17% and 30%, respectively (2). In our study, 22.4% of term infants developed postnatal epilepsy.

Severe neurological defects may occur in patients with neonatal convulsions including impairment of neurodevelopment, initiation of synaptic reorganization, altered plasticity, molecular reorganization of receptors and channels and development of epilepsy with increased brain injury (21). We identified an etiological factor in all of the patients with moderate/severe deficits in neurological examination. Additionally, we found that 85.4% of the patients with normal neurological findings or mild neurological deficit did not develop epilepsy but 62.5% of the patients with moderate/severe neurological deficit developed epilepsy. A statistically significant association was observed between neurological findings and the risk of developing epilepsy.

Patients with normal imaging results were reported to have a better prognosis than patients with imaging results showing severe deficits. Studies existed in the literature showed that diffuse abnormalities on MRI and CT scans are found to be 100% correlated with a poor prognosis and 66% of the patients with diffuse abnormalities were developed epilepsy (22,23). A retrospective review of the medical charts of our patients showed that 26.5% of the patients did not undergo ultrasound examination and MRI examination was not being performed in 38.8% of patients. Thus, no significant relation was found between the development of epilepsy and USG findings or MRI findings at follow-up.

Mortality and other poor outcomes were found in the majority of patients with moderate or severe EEG abnormalities. Moderate or severe EEG abnormalities were reported to be an important prognostic factor for epilepsy, developmental delay and cerebral palsy (12-14,24). Ninety-six percent of the patients with normal neonatal EEG findings and 90.48% of patients with normal follow-up EEG findings had normal neurological examination or mild neurological deficit. Although there was no significant association between neonatal EEG findings and the occurrence of epilepsy, follow-up EEG findings were found to be significantly associated with the development of epilepsy. Epilepsy did not occur in 86.4% of the patients with normal follow-up EEG results. Demonstration of the electrical seizures that reflect most of the seizure start in newborns through continuous monitoring would be a value in future studies.

In clinical trials, patients who do not receive any benefit from antiepileptic treatment were found to develop epilepsy in later life as reported by clinical trials (9,19). In our study, 67.3% of the patients starting on antiepileptic therapy at presentation benefited from treatment. Consistent with literature, a low rate of epilepsy (15.2%) was found in the patients deriving benefit from initiation of treatment and all of the patients who did not receive any benefit from treatment developed epilepsy. Among patients who did not experience recurrent seizures and not deemed to require treatment, none of them developed epilepsy at follow-up.

In conclusion, neonatal convulsions are one of the most common symptoms of acute neurological disorders in the neonatal period. Several researchers have proposed a scoring system to be able to demonstrate the effects of neonatal seizures on epilepsy and neurodevelopmental outcomes. However, most of the studies were limited due to short follow-up periods. More information is needed on this issue.

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