European Review for Medical and Pharmacological Sciences 2023; 27: 1384-1390

# The role of metabolic diseases in neonatal convulsions

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**Abstract. – OBJECTIVE: The neonatal period is the most vulnerable time for the development of seizures, particularly in the first weeks after birth. These seizures often signify serious malfunction or damage to the immature brain and constitute a neurological emergency, necessitating urgent diagnosis and management. This study was performed to identify the etiology of convulsions during the neonatal period and to determine the rate of congenital metabolic disease.**

**PATIENTS AND METHODS: A total of 107 term and preterm infants 0-28 days old who were treated and followed-up in the neonatal intensive care unit of our hospital between January 2014 and December 2019 were analyzed retrospectively based on data obtained by scanning the hospital information system and patient files.**

**RESULTS: The study population included 54.2% male infants, and 35.5% of infants were born by caesarean section. Birth weight was 3,016 ± 560 (1,300-4,250) g, mean length of gestation was 38 (29-41) weeks, and mean maternal age was 27.4 ± 6.1 (16-42) years. Of the infants, 26 (24.3%) were preterm and 81 (75.7%) were term deliveries. Examination of family history revealed 21 (19.6%) cases with consanguineous parents and 14 (13.1%) cases with a family history of epilepsy. Hypoxic ischemic encephalopathy was the most common etiology of the seizures (34.5%). Burst suppression was detected on amplitude integrated electroencephalography in 21 (56.7%) monitored cases. Although subtle convulsions were most common, myoclonic, clonic, tonic and unclassified convulsions were also observed. The convulsions appeared during the first week of life in 66.3% of cases and during the second week or later in 33.7%. Fourteen (13.1%) patients examined by metabolic screening due to suspected congenital metabolic disease had a different congenital metabolic diagnosis.**

**CONCLUSIONS: Although hypoxic ischemic encephalopathy was the most common cause of neonatal convulsions in our study, congenital metabolic diseases with autosomal recessive inheritance were detected at a high rate.**

*Key Words:*
Metabolic disease, Convulsion, Newborn.

## Introduction

Convulsion is a neurological dysfunction that occurs due to sudden, paroxysmal depolarization of neurons and is a clinical reflection of neurological problems that are common during the first month of life[1,2]. While the incidence of convulsions is 1-3/1,000 live births in mature infants, the rate is approximately 10 times higher in premature infants[3-5]. Neonatal convulsions are generally caused by hypoxic ischemic encephalopathy (HIE), intracranial hemorrhage, central nervous system infections, central nervous system congenital malformations, cerebrovascular incidents, drugs, acute metabolic disorders and congenital metabolic diseases. Acute symptomatic neonatal convulsions result from acute brain injury, whereas neonatal onset epilepsy may be associated with underlying structural, metabolic or genetic disorders. Convulsions associated with acute metabolic disorders develop due to hypoglycemia, hyponatremia/hypernatremia, hypocalcemia and hypomagnesaemia. Congenital metabolic diseases account for 3-7% of cases of neonatal convulsions[6,7]. They usually present with signs of acute encephalopathy during the neonatal period and may be caused by urea cycle defects, amino and organic acidemias, and oxidative phosphorylation defects. According to clinical findings, they are classified as subtle, clonic, tonic and myoclonic convulsions. As the synaptic connections are not fully mature, tonic-clonic convulsions do not occur during the neonatal period. Although there is no consensus regarding the optimal diagnosis algorithm, it is important to take clinical symptoms, physical examination, anamnesis and family history into



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account. Blood glucose and electrolyte levels, cranial imaging, electroencephalography (EEG) and amplitude integrated EEG (aEEG) are important for diagnosis. Blood ammonia, ketone, amino acid, carnitine and acyl carnitine levels, as well as urinary organic acid and reductant levels should be analyzed along with genetic testing to determine the etiology of convulsions caused by metabolic diseases. The galactose-1-phosphate uridylyltransferase level and long-chain fatty acid profile are diagnostically important for galactosemia and fat oxidation defects, respectively[8].

This study was performed to examine the demographic characteristics, clinical findings, laboratory and cranial imaging results of patients followed-up in the neonatal intensive care unit (NICU) with a diagnosis of convulsion based on a retrospective review of patient files, and to compare the rates of metabolic diseases and data in the literature to determine the etiology of convulsions.

## Patients and Methods

In this study, 107 term and preterm infants 0-28 days old who were treated and followed-up in the NICU of our hospital between January 1, 2014 and December 31, 2019 were retrospectively analyzed based on data from the hospital information system and patient files. Infants with non-epileptic paroxysmal events, such as jitteriness, benign neonatal sleep myoclonus, neonatal dystonia/dyskinesia, non-convulsive apnea and hyperexplexia, were not included in the study. Data from patient files, including sex, week of birth, type of birth, birth weight, family history of epilepsy, parental consanguinity, laboratory findings, imaging results, treatments received and anticonvulsant treatments, were examined.

The HIE stage was determined using the Sarnat scale. Hypoglycemia was defined as a blood glucose level < 40 mg/dL during the first 24 h after birth and < 50 mg/dL during the next 24 h.

Hypocalcemia was defined as blood calcium level < 8 mg/dL in term infants and < 7 mg/dL in preterm infants. Hypernatremia was defined as a serum sodium level ≥ 150 mg/dL. Hypomagnesaemia was defined as serum magnesium level < 1.6 mg/dL. The blood ammonia level was measured in cases with suspected congenital metabolic disease, and infants with an ammonia level > 150 μg/dL were considered to have hyperammonemia. In these cases, blood ketone, amino acid, carnitine and acyl carnitine levels, as well as urinary organic acid levels, were examined. The galactose-1-phosphate uridylyltransferase level was examined to determine a galactosaemia diagnosis (normal value 4-12 μmol/mL). After excluding congenital heart disease and pathologies that may cause a high lactate level, the lactate/pyruvate ratio was measured in cases with suspected congenital lactic acidosis. A lactate/pyruvate ratio < 25 was defined as normal, while a lactate/pyruvate ratio > 30 was considered to indicate pyruvate carboxylase deficiency.

As an indicator of infection, the blood C-reactive protein (CRP) level, blood culture and leucocyte count were evaluated. Lumbar puncture was performed after cranial imaging in patients with suspected central nervous system (CNS) infection. Growth in cerebrospinal fluid (CSF) culture, leucocyte count, and protein and glucose levels in CSF were examined, and cell counts were performed using a Thoma slide for direct microscopic examination of CSF samples. A leucocyte count > 10 $mm^3$ and increase in protein level were defined as a CNS infection.

Control transfontanelle ultrasonography was performed in all of our patients during the first 48 h and at the end of the first week of life. With the exception of five infants in critical general condition who were intubated and followed-up on a mechanical ventilator, computed tomography and/or magnetic resonance imaging (MRI) were performed in all cases. The definitive diagnosis of a CNS developmental anomaly was made by MRI.

### Statistical Analysis

Statistical analyses were performed using SPSS version 23.0 for Windows (IBM Corp., Armonk, NY, USA). Data normality was assessed by examining histograms and skewness and kurtosis values in the range of -1.5 to +1.5. Descriptive statistics for continuous variables are presented as the mean ± standard deviation (SD) for parametric data and the median (minimum-maximum) for nonparametric data. The Chi-square test was used to compare categorical variables in binary groups, and Student's *t*-test was used to compare normally distributed variables. The Mann-Whitney U test was performed for continuous variables that did not show a normal distribution. In all analyses, $p < 0.05$ was taken to indicate statistical significance.

**Table I.** Demographic characteristics.

| | | N = 107 | (%) |
|---|---|---|---|
| Male | | 58 | 54.2 |
| Female | | 49 | 45.8 |
| Type of birth | Normal birth | 69 | 64.5 |
| | Cesarean section | 38 | 35.5 |
| Birth time, weeks | | 38 (min 29-max 41) | |
| Birth weight, g | | 3,016 (min 1,300-max 4,250 gram) | |
| Maternal age, years | | 27.4 (min 16-max 42) | |
| Consanguineous marriage | | 21 | 19.6 |
| Epilepsy rate in the family | | 14 | 13.1 |

## Results

The study population included 54.2% male infants and 45.8% female infants; 35.5% infants were born by caesarean section. Birth weight was 3,016 ± 560 (1,300-4,250) g, mean length of gestation was 38 (29-41) weeks, and mean maternal age was 27.4 ± 6.1 (16-42) years. Of the infants, 26 (24.3%) were preterm and 81 (75.7%) term deliveries. The demographic characteristics are presented in Table I.

The mean APGAR scores at 1 and 5 min were 6 and 9, respectively. Examination of family history revealed 21 (19.6%) cases with consanguineous parents and 14 (13.1%) cases with a family history of epilepsy. HIE was the most common etiology of seizures (34.5%) (Table II). Thirty-seven infants who had active hypothermia for 72 h due to HIE were monitored by aEEG and followed-up. Burst suppression was detected on aEEG in 21 (56.7%) of these cases, and no pathological findings were detected in the remaining 16 (43.3%) cases. Results consistent with epileptic activity were obtained in 18 (16.8%) cases examined by EEG. Although most cases showed subtle convulsions, there were also cases of myoclonic, clonic, tonic and unclassified convulsions (Table III). Periventricular leukomalacia was detected most frequently by cranial imaging (Table IV). Convulsions appeared during the first week in 66.3% of cases and during the second week or later in 33.7%. The average hospital stay was 4 days (6 h to 18 days). Patients referred from other centers with suspected metabolic disease

**Table II.** Etiological causes.

| | | N (%) |
|---|---|---|
| Metabolic disorders | Hypoglycemia | 6 (5.6%) |
| | Hypo/hypernatremia | 7 (6.5%) |
| | Hypomagnesemia | 1 (0.9%) |
| | Hypocalcemia | 5 (4.7%) |
| Hypoxic ischemic encephalopathy | Stage 1 | 16 (14.9%) |
| | Stage 2 | 15 (14%) |
| | Stage 3 | 6 (5.6%) |
| Cerebral anomaly | | 2 (1.9%) |
| Intracranial hemorrhage | | 10 (9.3%) |
| Congenital Metabolic disease | Urea cycle defect | 3 (2.8%) |
| | Non-ketotic hyperglycinemia | 3 (2.8%) |
| | Organic acidemia | 2 (1.9%) |
| | Maple Syrup Urine Disease (Msud) | 1 (0.9%) |
| | Long chain fatty acid oxidation defect | 1 (0.9%) |
| | Galactosemia | 1 (0.9%) |
| | Congenital lactic acidosis | 1 (0.9%) |
| | Mitochondrial cytopathy | 1 (0.9%) |
| | Transient Hyperammonemia | 1 (0.9%) |
| B6 (Pyridoxine) deficiency | | 1 (0.9%) |
| CNS infection/Sepsis | | 7 (6.5%) |
| Idiopathic | | 9 (8.4%) |
| Family | | 8 (7.5%) |

**Table III.** Types of convulsions.

| | |
|---|---|
| Subtle | 56 (52.4%) |
| Myoclonic | 19 (17.8%) |
| Clonic | 17 (15.9%) |
| Tonic | 10 (9.3%) |
| Undefined | 5 (4.6%) |

had the longest mean hospital stay (7 days). Congenital metabolic disease positivity was found in 14 (13.1%) patients in metabolic screening performed in cases with suspected congenital metabolic disease.

Continuous venous-venous hemodiafiltration was performed in three patients, and peritoneal dialysis was performed in two patients. While the mortality rate was 5.6% in patients followed-up due to convulsions, the patients diagnosed with metabolic disease had a mortality rate of 35.7%. Elevated blood ammonia, alanine aminotransferase and aspartate aminotransferase levels were significantly correlated with an increased likelihood of metabolic disease.

## Discussion

Convulsion is an important clinical finding that arises due to brain dysfunction, requires urgent treatment and causes morbidity and mortality during the neonatal period. Previous studies[7,9] reported different convulsion rates in term and preterm neonates. Spagnoli et al[10] reported that convulsions occurred more frequently in preterm neonates, while Nair et al[11] reported that 69.3% of convulsion cases occur in term infants. In the present study, convulsions were most frequent in term infants (76%). In evaluations of neonatal convulsions, maternal age, family history of epilepsy, diabetes, previous infection, fetal distress syndrome, preterm birth, caesarean section and male sex were defined as risk factors[12-14]. Das and Debbarma[15] reported a male/female ratio of neonatal convulsions of 1.7:1. Consistent with the study of Al Naddawi et al[16], this ratio was 1.2:1 in the present study. In our study, 54.2% of patients were male and 45.8% were female, and 35.5% were delivered by caesarean section, while two cases were associated with a known high-risk maternal age. In a previous study[7] conducted in Turkey, 22% of neonatal convulsion patients had a familial history of convulsion; this rate was 13.1% in our study. While consanguineous marriages are common in our region, the rate of parental consanguinity was 19.6% in our study. Genetic factors should be taken into consideration when evaluating the etiology of neonatal convulsions. Although many mutations have been reported[17], the most common being KCNQ2 mutations causing epilepsy and providing familial transmission, their relationships with neonatal convulsions have not been elucidated in detail. Genetic analysis of patients with neonatal seizures of unknown etiology and detailed family history will provide important insights regarding the emergence of idiopathic convulsions. Subtle type seizures were reported[18,19] to be the most common type in neonates. In a study performed in a population of 77 neonates in India, Taksande et al[20] reported 24 (31.1%) cases of subtle type seizures, 36 (46.7%) of clonic type, 15 (19.4%) of tonic type and 2 (2.5%) of myoclonic type. Shah et al[21] defined subtle type seizures as the most common (39.6%) in their study in Pakistan. Consistent with the literature, subtle type seizures were the most common in our study, followed by tonic seizures. Similar results have been reported in previous studies[22,23]. In our study, convulsions occurred between the first 24 h and 7 days of life in term infants *vs.* after 7 days in preterm infants. These findings were consistent with a previous study[11], which reported that the onset time of convulsions was later in preterm infants. Whereas convulsions occurred within the first 24 h in all neonates with HIE stage 3 and 46.6% of those with HIE stage 2, they occurred between day 2 and 7 in the remaining patients with HIE. In term infants with hypocalcemia, hypoglycemia and other metabolic disorders, convulsions began within the first 24-72 h of life. The results of the present study were consistent with the literature[20,24,25] and showed that the onset of convulsions due to HIE occurred earlier, while convulsions due to bleeding and infection appeared at later stages. It has been reported[4] that seizures due to intraventricular hemorrhage in preterm neonates may occur on the first day, and most occur within 2-7 days after birth.

Convulsions occurred during the first 24 h in one case with a diagnosis of congenital metabolic disease and in one case of nonketotic hyperglycinemia with an amino acid metabolism disorder

**Table IV.** Magnetic Resonance Imaging findings.

| | |
|---|---|
| Normal result | 45 (44.1%) |
| Periventricular leukomalacia | 19 (18.6%) |
| Basal ganglion, thalamic lesion | 16 (15.8%) |
| Intraventricular hemorrhage | 9 (8.8%) |
| Non-specific changes | 13 (12.7%) |

in this study. In other patients diagnosed with congenital metabolic disease, the first seizures occurred an average of 5 (2-14) days after birth. Our patients diagnosed with intoxication type congenital metabolic disease accompanied by encephalopathy showed convulsion types that were more resistant to anti-epileptic drugs.

HIE was the most common etiology in both term and preterm newborn infants in the present study. In contrast, Moayedi et al[18] and Arpino et al[26] reported that hypoxic ischemic encephalopathy was the most common cause of convulsions during the neonatal period, and Taksande et al[20] reported that infections were the most common cause of neonatal convulsions, at a rate of 28.2%. In another study[27] conducted in 2000, the most common cause of convulsions during the neonatal period was reported to be HIE, with a rate of 35% in term infants. In a study[29] involving term and preterm neonates conducted in Turkey, perinatal asphyxia (28.6%) and intracranial hemorrhage (17%) were found to be the most common causes of neonatal convulsions. In a prospective study[28] conducted in California in 2016, the etiologies of neonatal convulsions were HIE (38%), ischemic attack (18%), intracranial hemorrhage (12%), epileptic encephalopathy/genetic epilepsy (6%), central nervous system infection (4%), metabolic disorders (hypoglycemia and other metabolic disorders) (4%), congenital metabolic diseases (3%), benign familial epilepsy (3%) and idiopathic convulsions (9%). Consistent with the literature, HIE was observed most frequently in our study (34.5%), and the frequency of intracranial hemorrhage was significantly higher in preterm than term neonates with convulsions.

In contrast to the rate of 4% reported by Glass et al[6], Besnili et al[7] reported a rate of hypoglycemic convulsions of 14.6%. Other studies[19,29] have also reported that hypoglycemia is more common in low-birth weight infants. On the other hand, Bhatt et al[30] reported that hypoglycemia was common in low-birth weight infants, and most cases were accompanied by intrauterine growth retardation. In our study, the rate of convulsions due to metabolic disorders, which was the second most common etiology, was 16.8%, consisting of hypernatremia/hyponatremia (6.5%), hypoglycemia (5.6%), hypocalcemia (4.7%) and hypomagnesemia (0.9%). This may have been because our hospital serves a region of low socioeconomic development, with more patients referred from neighboring provinces and issues related to inadequate care and nutrition. The role of CNS infections in the etiology of neonatal convulsions varies among countries depending on the level of development. CNS infection rates of 4-8.2% have been reported[6,20] in different counties. In our country, the rate of CNS infections is reportedly 4.8%. In the present study, CNS infection and sepsis were found to contribute to the etiology of convulsion in 6.5% of patients, which was lower than the corresponding rates of 17.2-28.7% in some developing countries[31,32]. The rates of CNS infection and sepsis vary among countries depending on the level of development.

In a study[6] conducted in the USA, the rate of intracranial bleeding as an etiological factor of neonatal convulsions was reported to be 12%. However, studies[7,31,33] conducted in Iran and Turkey reported rates of 6.9% and 2.4%, respectively. The incidence of intracranial hemorrhage, which is more common in preterm newborn infants, was 9.3% in our study. The reason for the differing rates of intracranial hemorrhage can be explained by the average body weight of the infants included in the studies; the risk of intracranial hemorrhage may be higher in preterm and low weight infants than in those born with normal weight, which may be related to the weight of the infants and level of vascular maturation.

Congenital metabolic diseases with reported incidence rates of 3-7.3% across studies[6,7] are among the causes of convulsions in neonates. The rate of congenital metabolic diseases in the present study was 13% higher than the corresponding rates in the literature. As most congenital metabolic diseases show an autosomal recessive inheritance pattern, they are encountered more frequently in societies with higher rates of consanguineous marriages[34]. Kulalı et al[35] reported that 57.6% of patients with congenital metabolic disease had consanguineous parents. The risk of congenital metabolic disease is increased in patients with a history of consanguineous parents and of sibling death of unknown cause. In a two-center study conducted in 2014 in Oman, Al-Thihli et al[36] documented that 95% of 285 patients diagnosed with congenital metabolic disease had consanguineous parents. In the present study, the rate of parental consanguinity among infants with metabolic disease was 37.1%. Patients diagnosed with congenital metabolic diseases appear healthy at birth, as the intermediate metabolites responsible for these diseases are small molecules that pass through the placenta and can be removed by maternal metabolism. Therefore, almost all of our patients

were delivered after a normal gestation period (93%) and had a normal birth weight (86%). Further comprehensive studies are required to examine the relationships between congenital metabolic diseases and parental consanguinity. The blood ammonia level plays an important role in the diagnosis of congenital metabolic diseases[37]. In the present study, the blood levels of alanine aminotransferase and aspartate aminotransferase were significantly elevated. Continuous venous-venous hemodiafiltration was performed in three of our patients, and peritoneal dialysis was performed in two of these patients with severe encephalopathy with an ammonia level > 1,000 μg/dL. The mortality rate in the present study was 5.6% among patients followed-up for convulsions, but 35.7% in patients with a diagnosis of metabolic disease. The occurrence of convulsions was reported[6] to be associated with increased morbidity and mortality rates in both term and preterm neonates. The parents and siblings of 7.5% of our patients had a history of epilepsy. The incidence of idiopathic convulsions was 8.4% in our study population, which was within the rate range of 2.4-27% previously reported[38]. The rate of convulsions of unknown etiology may vary depending on the equipment available in clinics, the laboratory facilities and the presence of pediatric subspecialists. Comprehensive screening of congenital metabolic diseases and genetically transmitted diseases will be beneficial for diagnosis and treatment of newborn convulsions of unknown etiology, especially in societies where consanguineous marriages are common.

## Conclusions

The results of the present study showed that HIE was the most common cause of neonatal convulsions, followed by metabolic disorders. The rate of congenital metabolic diseases was high. Early consideration of congenital metabolic diseases is very important for early diagnosis, and delayed diagnosis can lead to sequelae and even death. Comprehensive metabolic screening and genetic analyses are required to evaluate convulsions of unknown etiology in regions with a high rate of consanguineous marriage.

### Conflict of Interest
The Authors declare that they have no conflict of interests.

### Ethics Approval
This study was approved by the Ethics Committee of SBU Diyarbakir Gazi Yaşargil Training and Research Hospital Ethics Committee (2021/954).

### Authors' Contribution
Study concept and design: S.S.; acquisition of data: S.S. and M.C.; analysis and interpretation of data: O.A.; drafting of the manuscript: M.C.; critical revision of the manuscript for important intellectual content: M.C.; statistical analysis: O.A.; administrative, technical, and material support: İ.D. and N.Ö.; study supervision: M.C.

### Informed Consent
Written informed consent was obtained from all participants' parents or legal guardians.

### Funding
None.

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