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Original article

Investigating and determining the risk factors of neonatal seizures in NICU patients in the South of Iran

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Abstract

Introduction: The incidence of neonatal seizures has been reported at 1.8 to 8.6 in 1,000 live births. It seems that the brain of premature children is more susceptible to seizures. The causes of neonatal seizures comprise a range of neurological disorders, including hypoxic-ischemic encephalopathy (HIE), central nervous system infection, intracranial hemorrhage, and structural disorder of the brain. Among all, the most common cause is HIE. Given the risks and consequences of neonatal seizures, this study aimed to investigate their risk factors.

Methods: This is a descriptive cross-sectional study of 92 neonates, aged < 28 days, admitted to Neonatal Intensive Care Unit (NICU) during the period from March 2011 to May 2014, with the diagnosis of seizures. Demographic data including age, sex, gestational age, birth weight, fifth minute Apgar score were extracted from patient files. Data were analyzed using SPSS® version 19 software.

Results: Of 92 cases, 12 (13.0%) had the fifth minute Apgar score above 8, 79 (85.9%) had Apgar score between 3 and 8, and 1 (1.1%) had Apgar score less than 3. Asphyxia was present in 63 (68.5%) infants. Seizure types were clonic in 41 (44.6%) cases, myoclonic in 20 (21.7%) cases, of mild type in 14 (15.2%) cases, and tonic in 17 (18.5%) cases. Metabolic disturbances revealed hypoglycemia in 7.6%, hypocalcemia in 2.2%, hyponatremia in 4.3%. Hereditary metabolic disorders were observed in 6.5% of patients.

Conclusion: HIE was the most common cause of neonatal seizures, and cerebral hemorrhage and metabolic disorders were other two major causes

of seizures after HIE. The most common type of seizures was the clonic type. The results suggest that male gender and a postnatal age < 2 weeks are associated with an increased risk of seizure in normal and premature infants.

Keywords

Seizure, neonate, NICU, hypoxic-ischemic encephalopathy.

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Introduction

Seizures, as a symptom of central nervous system disease, are common in the neonatal period, and may be the first sign of neonatal dysfunction [1]. The incidence of neonatal seizures has been proposed at 1.8 to 8.6 in 1,000 live births. However, there are significant differences in the reported statistics. This can be related to the problem of diagnosis, different definitions of neonatal seizures, and the choice of the population to study [2]. A higher rate of seizures has been reported in premature neonates. It seems that the brain of the premature neonates is more susceptible to seizures, which could be due to the earlier evolution of stimulant synapses with dominant effects on the inhibitory synapses of the brain in the early stages of growth. Moreover, due to an increased risk of developing metabolic, toxic, infectious and structural diseases in this period of life, seizures in newborns pose a serious threat [3, 4].

The characteristics of neonatal seizures are unique. In the majority of cases, the diagnosis of neonatal seizures and its various causes is based on history and clinical risk assessment, and only a very small percentage of neonatal seizures is idiopathic [5]. Hypoxic-ischemic encephalopathy (HIE), central nervous system infection, intracranial hemorrhage, metabolic and structural disorder of the brain are the possible causes of neonatal seizures; among them, the most prevalent etiology is HIE [6, 7].

There are different types of neonatal seizures, but the most common type is focal and generalized tonic-clonic seizures (common seizures of older ages). The possible reason could be the premature structure of the brain, less cortical organization, and incomplete development of neonatal myelination. Moreover, neonatal seizures are not able to sustain continuous and frequent activities for a long time due to immaturity of the neonate, and therefore neonatal seizures tend to be short-lived [4, 8].

Neonatal seizures have various effects on the baby's brain development, the process of DNA synthesis, the proliferation and differentiation of the glia, and myelination of the nerves. New studies on animals have shown that the neonatal nervous system may be partially resistant to long seizures, but short and repeated seizures may be associated with permanent damage to the central nervous system, increased risk of epilepsy and long-term cognitive impairment [9]. Furthermore, the harmful effects of seizures should always be compared to the potentially adverse effects of anticonvulsant drugs on the behavior and learning development of neonatal brain [5].

Further studies are required to identify the underlying cause of seizures, since many etiologies have specific treatments and might have better outcomes if treatment is taken earlier [1, 4, 6]. Moreover, in the absence of timely diagnosis and treatment, neonatal seizures could be associated with an increase in mortality rates and neurological complications. So, neonatal seizures are considered as an important factor in long-term prognosis [10, 11].

Considering the risks and consequences of neonatal seizures, the present study was conducted to investigate the risk factors of neonatal seizures in the Neonatal Intensive Care Unit (NICU) section of Ali-Ibn-Abitalib Hospital in Zahedan (Iran) during 2011-2014.

Methods

The present study was designed based on the Declaration of Helsinki and was approved by the Research Ethics Committee of the Zahedan University of Medical Sciences at license number: 6393. In this research, a descriptive cross-sectional study

was conducted in the NICU section of the Ali-Ibn-Abitalib Hospital in Zahedan and 102 neonates who were admitted to NICU during the period from March 2011 to May 2014 were registered. After examination and history performed by a pediatric neurologist, they were diagnosed with neonatal seizures, confirmed by electroencephalography (EEG) report in the Hospital Patient Record File. Seven cases were excluded due to incomplete files and 3 cases were excluded due to having a diagnosis other than neonatal seizures. Thus, 92 cases were studied.

Demographic data including age, sex, gestational age, birth weight, and fifth minute Apgar score were extracted from patient files. We used the results of clinical biochemistry tests for evaluating metabolic causes (such as hypocalcemia, hypoglycemia, hyponatremia, etc.), the brain imaging including ultrasound and/or magnetic resonance imaging (MRI) for radiologic findings (encompassing HIE, intracranial [intraparenchymal and intraventricular] hemorrhage, hydrocephalus, cerebellar malformation, etc.), cerebrospinal fluid analysis for meningitis and encephalitis, karyotype test for chromosomal anomalies, and TORCH screen for TORCH infections. Finally, we gathered all the etiologies together and evaluated them with the type of seizures.

At last, data were analyzed using SPSS® version 19 software. Descriptive analysis was used to present the results, including mean ± standard deviation (SD) for quantitative variables and frequency (percentage) for categorical variables.

Results

In this study, a total of 92 neonates admitted to the NICU department of Ali-Ibn-Abitaleb Hospital were studied. Of these, 48 (52.2%) were male, and 44 (47.8%) were female. The mean age of hospitalized infants was 8.76 ± 8.11 days, of which 67 (72.8%) neonates were less than 2 weeks old and 25 (27.2%) were older than 2 weeks old. The minimum age of the newborn was 1 day, and the maximum was 28 days. The mean birth weight in hospitalized infants was 2,692 ± 703 grams. Sixty-four (69.6%) neonates were weighing more than 2,500 grams and 28 (30.4%) neonates weighing less than 2,500 grams. The minimum weight in the neonates was 1,000 grams and the maximum was 3,900 grams.

The gestational age in newborns showed that 13 (14.1%) neonates were preterm, 77 (83.7%) neonates were term and 2 (2.2%) neonates were post-term. The mean of fifth minute Apgar scores in hospitalized infants was 6.96 ± 2.29. Twelve (13.0%) of the newborns had Apgar score greater than 8, 79 (85.9%) had Apgar score between 3 and 8, and 1 (1.1%) had Apgar score less than 3. The lowest Apgar score was 3 and the maximum 10. Asphyxia examination showed that there was asphyxia in 63 (68.5%) neonates (**Tab. 1**).

Investigating the causes of seizures showed that the common causes were HIE (40.2%), cerebral hemorrhage (18.5%), hypoglycemia (7.6%), meningitis (6.5%), hereditary metabolic disorders (6.5%), hyponatremia (4.3%), TORCH (3.3%), hydrocephalus (3.3%), cortical malformations (2.2%), hypocalcemia (2.2%); in 5.4% of the cases, the causes of seizures were uncertain (**Tab. 2**). None of the newborns had hypomagnesemia or B6 deficiency (**Tab. 2**).

Seizure types in 92 neonates showed that 41 (44.6%) cases were of clonic type, 20 (21.7%) cases of myoclonic type, 14 (15.2%) cases were mild and 17 (18.5%) cases were of tonic type (**Tab. 3**).

Table 1. Asphyxia frequency in newborns admitted to Neonatal Intensive Care Unit (NICU).

Asphyxia	Number	Percentage
Yes	63	68.5
No	29	31.5
All	92	100

Table 2. Frequency of causes of seizures in newborns admitted to Neonatal Intensive Care Unit (NICU).

Causes of seizures	Number	Percentage
HIE	37	40.2
Cerebral hemorrhage (intraparenchymal and intraventricular)	17	18.5
Hypoglycemia	7	7.6
Meningitis	6	6.5
Hereditary metabolic disorders	6	6.5
Hyponatremia	4	4.3
TORCH	3	3.3
Hydrocephalus	3	3.3
Cortical malformations	2	2.2
Hypocalcemia	2	2.2
Unknown	5	5.4
All	92	100

HIE: hypoxic-ischemic encephalopathy.

Table 3. Frequency of seizures in newborns admitted to the Neonatal Intensive Care Unit (NICU).

Seizure type	Number	Percentage
Clonic	41	44.6
Myoclonic	20	21.7
Mild	14	15.2
Tonic	17	18.5
All	92	100

The frequency of causes of seizures classified by seizure type is as follows (**Tab. 4**):

- in clonic type seizures, cerebral hemorrhages, including intraparenchymal and intraventricular hemorrhages, (34.1%) and HIE (31.7%) are the most common causes of seizures;
- in myoclonic type seizures, HIE (60%) and meningitis (20%) are the most common causes of seizures;
- in cases of mild type seizures, HIE (42.9%) and TORCH (21.4%) are the most common causes of seizures;
- in cases of tonic type seizures, HIE (35.3%) and hereditary metabolic disorders (29.5%) are the most common causes of seizures.

Discussion

The present study investigated the risk factors of neonatal seizures in a total of 92 neonates who were admitted to the NICU department of Ali-Ibn-Abitaleb Hospital, Zahedan. In our sample, 48 (52.2%) infants were male and 44 (47.8%) neonates were female. Our data showed that the mean birth weight was 2,692 grams and 30.4% were low birth weight. The study of gestational age showed that 77 (83.7%) neonates were term, 13 (14.1%) neonates were preterm, and 2 (2.2%) newborns were post-term. The mean Apgar score at 5 minutes was 6.96; 12 (13.0%) of the newborns had Apgar score above 8, 79 (85.9%) had Apgar score of 3-8 and 1 (1.1%) had Apgar score less than 3.

Similar to our study, Abbaskhanian et al. studied 99 (57%) female neonates and 75 (43%) male neonates at Sari hospitals (Sari, Iran) to investigate the prevalence of seizures and related factors in hospitalized infants. In terms of gestational age, 73 (42%) neonates were above 37 weeks, and 101 (58%) neonates were preterm. In terms of weight, 100 (57%) neonates were low birth weight. The mean age of neonates was 8 days, of which 127 (73%) neonates were less than 2 weeks old and 47 (27%) neonates were older than 2 weeks. Also, 94 (54%) had the first 5 minutes Apgar score upper 8, 44 (25%) had Apgar score between 3 and 8 and 36 (21%) had Apgar score less than 3. This study showed that prematurity and low birth weight were important risk factors for neonatal seizures. Low Apgar score might be due to physiological immaturity in preterm neonates [12].

Moreover, Saliba and colleagues conducted a study at the University of Texas (Houston, Texas, USA) on 207 neonatal seizures, to determine their risk and their association with birth weight, gender, ethnicity, place of birth, maternal age, and types of delivery. For preterm infants, very low birth weight (< 1,500 grams) was the strongest risk factor of seizure, and for term neonates, the common risk factors of seizure were cesarean delivery, low birth weight and maternal age of 18-24 years old [13].

Based on another study, maternal morbidity in the 2 years before pregnancy, more than 14 kg of maternal weight gain during pregnancy, pathology of the placenta, preeclampsia, low birth weight, low gestational age and jaundice in the first 3 days of life were possible risk factors for neonatal seizures [14].

These studies were consistent with our research in terms of gender distribution and the age of neonatal

Table 4. Comparison of the frequency of causes and types of seizures in newborns admitted to the Neonatal Intensive Care Unit (NICU).

Seizure cause	Seizure type				All
	Clonic	Myoclonic	Mild	Tonic	
HIE	13 (31.7%)	12 (60%)	6 (42.9%)	6 (35.3%)	37 (40.2%)
Cerebral hemorrhage (intraparenchymal and intraventricular)	14 (34.1%)	-	-	3 (17.6%)	17 (18.5%)
Hypoglycemia	-	2 (10%)	2 (14.3%)	3 (17.6%)	7 (7.6%)
Meningitis	2 (4.9%)	4 (20%)	-	-	6 (6.5%)
Hereditary metabolic disorders	1 (2.4%)	-	-	5 (29.5%)	6 (6.5%)
Hyponatremia	2 (4.9%)	2 (10%)	-	-	4 (4.3%)
TORCH	-	-	3 (21.4%)	-	3 (3.3%)
Hydrocephalus	3 (7.3%)	-	-	-	3 (3.3%)
Cortical malformations	2 (4.9%)	-	-	-	2 (2.2%)
Hypocalcemia	2 (4.9%)	-	-	-	2 (2.2%)
Unknown	2 (4.9%)	-	3 (21.4%)	-	5 (5.4%)
All	41 (100%)	20 (100%)	14 (100%)	17 (100%)	92 (100%)

HIE: hypoxic-ischemic encephalopathy.

seizures. However, due to the lack of other risk factors such as maternal age and types of delivery in this study, the results were not comparable.

As expected and consistent with prior findings [15-18], our results showed that 40.2% of the neonates suffered from HIE, and 18.5% were related to cerebral hemorrhage. Moreover, hypoglycemia (7.6%), meningitis (6.5%), central nervous system abnormalities (5.4%), hereditary metabolic abnormalities (6.5%), hyponatremia (4.3%), TORCH (3.3%), hypocalcemia (2.2%) were the possible causes of seizures. Asphyxia was present in 63 infants (68.5%).

In Tekgul et al.'s study, 89 infants with seizures were evaluated and, among them, the cause of seizures of 77 cases was identified. The brain ischemia-generalized hypoxia (40%), cerebral ischemia-hypoxia (18%) and cerebral hemorrhage (17%) were the most common causes [19].

A study in Ahvaz (Iran) was conducted to determine the causes of neonatal seizures and its relation with age, sex, and birth weight and types of delivery. Ninety-four newborn infants with primary diagnosis of neonatal seizures were admitted to Imam Khomeini Hospital and Ahvaz Hospital during three years; 79% of these newborns suffered from seizures in the first 14 days of life. HIE (34%), intracranial hemorrhage (13%), hypoglycemia (10%), meningitis (6%), hypocalcemia (3%), and hereditary metabolic disorders (3%) were the origins of neonatal seizures, and in 31% of cases no etiology was found [20].

The results of these studies were consistent with our study in terms of the prevalence of seizures.

In our study, 41 (44.6%) infants had clonic seizures, 20 (21.7%) cases showed myoclonic type, 14 (15.2%) cases had a mild type of seizures and in 17 (18.5%) cases the seizures were of tonic type.

In the study of Arpino et al., diffuse tonic seizures (29%) were the most common type of seizures. The most common cause of neonatal seizures was HIE (30%) [14].

According to results of Abbaskhanian et al., the most common type of seizures was focal seizures (67, 38.5%), followed by mild seizures (36 cases, 20.7%), myoclonic (29, 16.7%), generalized tonic-colonies (22, 12.6%) and a combination of the above (20, 11.5%) [12].

In our study, metabolic disturbances revealed that hypoglycemia, hypocalcemia, hyponatremia, and hereditary disorders were present in 7.6%, 2.2%, 4.3% and 6.5%, respectively.

In conclusion, HIE was the most common cause of neonatal seizures, and cerebral hemorrhage and metabolic disorders were the other two major causes of seizures after HIE. The most common type of seizures was of clonic type. The results suggest that male gender and a postnatal age < 2 weeks are associated with an increased risk of seizure in normal and premature infants.

Ethics statement

The study was approved at the Zahedan University of Medical Sciences Ethics Committee (Ethics code: 6393) and the requirement to obtain patients' consent to participate was waived, because the data were anonymous.

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The study was firstly approved by the Ethics and Research Committee of the Zahedan University of Medical Sciences.

Declaration of interest

The Authors declare that they have no conflicts of interest.

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