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Long-term outcome in children with neonatal seizures: A tertiary center experience in cohort of 168 patients

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ABSTRACT

Purpose: The purpose of this study was to evaluate long-term outcome and assess predictors of prognosis in children with neonatal seizures (NS).
Method: This retrospective study includes children with NS treated at our Institute from January the 1st 2005 until December the 31st 2015. The data were collected from medical charts and the electroencephalogram (EEG) database at the Institute. The predictive value was evaluated for following parameters: (1) characteristics of the patients, such as gender, gestational age, birth body weight, Apgar score, artificial ventilation; (2) etiology; (3) characteristics of seizures such as type, time of onset, resistance to treatment; and (4) EEG background activity and paroxysmal discharges. The outcome of NS was assessed at the end of the follow-up period and was categorized as one of the following: (1) lethal outcome, (2) neurological abnormalities, (3) intellectual disability, and (4) epilepsy. Univariate and multivariate logistic regression analyses were used to assess predictors of NS outcome.
Results: The study included 168 children with NS (of which 109 are males, and 59 are females), mean aged 5.6 (SD 3.5) years at the end of the follow-up (with a range of 1 to 12 years). There was normal neurological development without epilepsy in 131 patients (78%), neurological abnormality in 31 (19.0%), intellectual disability in 28 (17.2%), epilepsy in 12 (7.4%), and lethal outcome in 7 patients (4.17%).
Conclusions: Long-term outcome in children with NS could be favorable in most patients, and it appears to be related to specific early clinical and paraclinical variables. Newborns with an abnormal background EEG activity, with seizures resistant to antiepileptic drugs and/or low Apgar score are at a higher risk of a poor outcome. Females are at a much higher risk of lethal outcome than males.

1. Introduction

Neonatal seizures (NS) are the most common neurological disorder in newborns, and often the first sign of neurological dysfunction. The seizures in neonatal period are the topic of many scientific and clinical investigations due to their powerful predictor value of long-term cognitive and developmental impairment. The etiology of NS is very heterogeneous, mostly acute symptomatic. It is very important to determine causes of NS, since etiology has significant impact on prognosis and outcome and influences further therapeutic strategies [1–3].

Neonatal seizures are mostly focal, though generalized seizures have also been described in rare instances, and their clinical presentation highly variable. One particular type of NS are so-called "subtle seizures", which are clinically manifested as chewing, pedaling, and/or ocular movements, that are more common in full-term than in premature infants [2,4]. The scoring system for an early prognostic assessment after NS was devised by Pisani et al. identifying independent risk factors for adverse outcome as follows: (1) weight at birth, (2) Apgar score at first minute, (3) neurological status at the seizure onset, (4) cerebral ultrasound findings, (5) efficacy of anticonvulsant therapy, and (6) the presence of neonatal status epilepticus [5].

The aims of this study were to evaluate the long-term outcome and to identify predictors of lethal outcome, neurological and intellectual disabilities and epilepsy in children with NS treated in tertiary hospital.

2. Methods

The retrospective study included children with NS treated at the Intensive Care Unit (ICU) and/or Department of Neurology at the Institute for Mother and Child Healthcare of Serbia during the period from January the 1st 2005 to December the 31st 2015.

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The inclusion criteria are as follows: (1) full-term and preterm newborns with seizures clinically observed by a physician in our hospital within the neonatal period, (2) newborns without clinically manifested seizures, but with an ictal electroencephalographic pattern of seizures, (3) newborns with EEG recording within the first 48 h after seizure onset, (4) duration of the follow-up for at least 12 months.

The exclusion criteria are as follows: (1) the children with a history of NS if their seizures were not noted during hospitalization at our Institute, (2) all children with NS with a follow-up shorter than 12 months, (3) newborns with NS but without EEG recording made within the first 48 h after the seizure onset.

The neonatal period is limited to the first 28 days of life in a full-term infant. In the case of premature infants, this term is usually applied until 44 weeks of gestation. Preterm newborn is any infant of less than 37 gestational weeks. The delivery is categorized as uncomplicated (spontaneous vaginal or planned Cesarean section) and complicated (vaginal with vacuum extraction and forceps or urgent Cesarean section due to fetal suffering). The newborns are divided into two groups according to their weight at birth: (1) less than 2500 g, and (2) more than 2500 g; and in three categories referring to their Apgar score (AS) during the first minute: (1) from 0 to 3, (2) from 4 to 7, and (3) from 8 to 10. Physical and neurological examination, hematological, biochemical and microbiological blood and urine analyses, cranial ultrasound, and electroencephalography were done in all newborns. Depending on the clinical presentation, additional investigations were done, such as: cerebrospinal fluid (CSF) analyses, serological analyses of blood and CSF, ultrasound of heart and abdomen, computerized tomography, and magnetic resonance. The following parameters and their impact on the outcome have been investigated: intubation and invasive supporting ventilation assistance, neurological finding at the time of seizure onset (before and after 48 h), the presence of status epilepticus, the type of seizures, EEG features (background and paroxysmal activity), and the response to the treatment. Status epilepticus is defined as continuous seizure activity for at least 30 min or recurrent seizures that lasted a total of 30 min without definite return to the baseline neurologic condition between seizures [6]. Neurological status was determined as normal or abnormal according to the following: muscle tone, spontaneous movement, state of consciousness during the newborn period [7], whereas an assessment at the end of the follow-up included a complete neurological examination. The seizures are classified according to their clinical manifestation as subtle, clonic, tonic, and myoclonic [8]. Electrographic seizures without clinical manifestation are separated in a particular category.

For etiological classification, we used the model by Mizrahi and Clancy [3]: (1) hypoxic ischemic encephalopathy (HIE) caused by one of the following: global perinatal, congenital heart disease, cardiopulmonary arrest, stroke, thrombosis, respiratory impairment; (2) toxic–metabolic and included: electrolyte disturbances, hypoglycemia, toxic effects of the drugs and abstinence syndrome; (3) systemic and intracranial infection; (4) intracranial hemorrhage; (5) inborn errors of metabolism; and (6) cerebral malformations.

All newborns were treated according to the standard hospital protocol for the treatment of seizures. The first line drug is phenobarbital in a single dose of 20 mg/kg, which could be repeated if the seizure continues or recurs. The second line drug is midazolam (range 0.1–1 mg/kg/h) if the newborn requires artificial ventilation. For newborns not needing artificial ventilation, depending on availability, the second line is phenytoin 18 mg/kg delivered intravenously or levetiracetam 30–60 mg/kg per nasogastric tube or intravenously. Intravenous infusion of pyridoxine is given in all cases with resistant seizures. Etiological treatment is obvious and starts immediately in all cases with an established cause of seizures.

A positive response to treatment is defined if the seizure stopped after application of the first or the second line drugs [9]. Electroencephalograms were performed within 48 h after the seizure. The electrodes were placed based on the 10–20 system as modified for newborns. The speed of recording was 30 mm/s, and we used the time constant of 0.3 s, sensitivity of 10 μv/mm, and high linear frequency filter of 70 Hz. The duration of recording was at least 60 min, and in the cases recorded after 2006, a video-EEG was performed if the conditions of newborn allowed prolonged stay in EEG laboratory at room temperature [10,11]. The EEG reporting was performed by a neurophysiologist trained for neonatal EEG reading, and two main features were analyzed: background activity (normal or abnormal) and paroxysmal discharges suggestive of epileptic activity (present or absent). Abnormal background activity (BA) included the following EEG patterns: (1) low amplitude; (2) slow frequency; (3) burst suppression pattern; (4) asymmetric BA in frequency and/or amplitude. The outcomes included lethal outcome, neurological abnormalities, intellectual disability, and the presence of epilepsy. The follow-up period lasted for at least 12 months, until the end of the study. The outcome assessment was done according to a neurological clinical examination, a psychometric testing by a psychologist and an electroencephalographic recording. Intellectual ability is evaluated according to the Brunet-Lezine scale. Intellectual disability (ID) is defined by an IQ score under 70 in addition to deficits in two or more adaptive behaviors that affect everyday life [12]. We used the definition of epilepsy recommended by the International League Against Epilepsy (ILAE) [13].

3. Stasistical analysis

Categorical variables were described by counts or percentages. The assumption of normality was tested by Kolmogorov–Smirnov test for continuous variable birth body weight and follow-up period). Test results showed normal distribution for birth body weight and the skewed distribution for follow-up period. Continuous variables were described by mean and standard deviation or median and interquartile range.

For logistic regression four dependent variables were observed: neurological abnormalities (1: absent, 2: present), intellectual disability (1: absent, 2: present), epilepsy (1: no, 2: yes), and lethal outcome (1: no, 2: yes). Independent variables included the following: gender (1: male, 2: female), gestational age (1: term, 2: preterm), birth body weight (1: >2500 g, 2: ≤2500 g), Apgar score 1st minute (1: 8–10, 2: 4–7, 3: 0–3), delivery (1: uncomplicated, 2: complicated), neurological finding at the time of NS (1: normal, 2: pathological), artificial ventilation (1: not used, 2: used), clonic seizures (1: absent, 2: present), tonic seizures (1: absent, 2: present), subtle seizures (1: absent, 2: present), myoclonic seizures (1: absent, 2: present), electrographic seizures (1: absent, 2: present), number of seizures type (1: one, 2: two or more), the seizure onset (1: first 48 h, 2: after 48 h), status epilepticus (1: absent, 2: present), EEG background activity (1: normal, 2: abnormal), EEG paroxysmal activity (1: absent, 2: present), resistance to the treatment (1: responsive to treatment, 2: resistant to treatment), HIE (1: absent, 2: present), toxic–metabolic (1: absent, 2: present), infections (1: absent, 2: present), hemorrhage (1: absent, 2: present), inborn errors of metabolism (1: absent, 2: present), and central nervous system (CNS) anomalies (1: absent, 2: present). The variables with a p-value of 0.01 on univariate analysis were included in a multiple logistic regression analysis. The probability 0.05 was taken as the minimum level of significance. Data were entered and analyzed using the SPSS v.22.

The study was approved by the Institutional Ethics Board.

4. Results

The retrospective study included 168 children with NS treated at the Institute during a period of 11 years. Most of our cohort are full-term newborns with body weight (BW) at birth higher than 2500 g. The average body weight at birth was 3285.7 g (min: 1750, max: 5450, SD: 597.787, med: 3300, iqr: 700), and in the group with body weight below 2500 g, the mean weight was 2149.3 g (min: 1750, max: 2430, SD: 225.541, med: 2160, iqr: 432.5). Neonatal seizures are more