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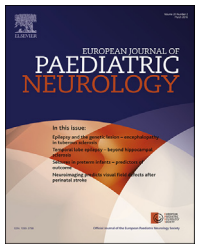

Original article

Neonatal seizures in preterm newborns: A predictive model for outcome

Francesco Pisani [a,*], *Carlotta Facini* [a], *Annalisa Pelosi* [b], *Silvia Mazzotta* [a], *Carlotta Spagnoli* [a], *Elena Pavlidis* [a]

[a] *Child Neuropsychiatry Unit, Neuroscience Department, University of Parma, Italy*
[b] *Psychometrics, Neuroscience Department, University of Parma, Italy*

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ABSTRACT

Background: With a reported prevalence of 22.2%, seizures in preterm newborns represent an emergent challenge, because they are often related to adverse outcome. The electro-clinical features of preterm infants with neonatal seizures were evaluated in order to predict outcome.

Methods: From 154 newborns with video-EEG confirmed neonatal seizures admitted to Parma University Hospital between January 1999 and December 2012, we collected 76 preterm newborns with neonatal seizures. Outcome was assessed at least at one year. Student t-test for unpaired data was used to compare means of continuous variables. We applied the χ^2 test to compare nominal data between preterm newborns with favorable versus adverse outcome, and between those with seizures versus those with status epilepticus. Then we determined the independent risk factors for adverse outcome with multivariate logistic regression analysis.

Results: Birth weight, Apgar at 1st minute, neurologic examination, EEG, US brain scans and the presence of neonatal status epilepticus were different between preterm newborns with favorable and adverse outcome ($p \leq .049$). Furthermore, birth weight, seizure onset, neurologic examination and EEG were different between the group with or without status ($p \leq .031$). None of the infants with status epilepticus had a favorable outcome compared to 22.3% of those with neonatal seizures ($p = .004$). We also identified a predictive model that correctly classified outcome in 85.5% of subjects, with a high sensitivity for adverse outcome (>91.5%).

Conclusion: The presence of neonatal seizures in preterm newborns is highly related to an adverse outcome that can be predicted since the first days of life.

Abbreviations: v-EEG, video-EEG; CUS, cerebral ultrasound; HIE, hypoxic–ischemic encephalopathy; IVH, intraventricular hemorrhage; NICU, neonatal intensive care unit; PVL, periventricular leukomalacia.

* *Corresponding author*. U.O. di Neuropsichiatria Infantile, Dipartimento Materno-Infantile, Azienda Ospedaliero-Universitaria di Parma, Via Gramsci 14, 43126 Parma, PR, Italy. Tel.: +39 (0) 521702205; fax: +39 (0) 521704708.
E-mail address: elena.pavlidis2@gmail.com (F. Pisani).

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1. Introduction

Seizures in preterm newborns represent an emergent challenge for clinicians also because of the increased survival rate of very early premature infants secondary to the progresses in perinatal care.[1,2] The EPICure studies have demonstrated an increase of 13% in survival to 3 years in babies born before 27 weeks gestation in 2006 compared to those born in 1995 in England.[3] Furthermore, the immature brain seems to be more prone to experience seizures in response to injury[4,5] with a prevalence of seizures in preterm infants reported as high as 22.2% compared to 0.5% in full-term newborns.[6] Seizures in newborns are more often symptomatic markers of brain injury[7] and the most common etiology of neonatal seizures in preterm newborns is intraventricular hemorrhage (IVH).[8–10] Seizures are often identified by clinical observation in these newborns without a synchronized video-EEG (v-EEG) monitoring with a risk of misinterpreting clinical phenomena due to less organized motor patterns compared to full term newborns.[11] Therefore, v-EEG monitoring is important for a prompt and reliable identification of neonatal seizures.[12] The etiology is thought to be the variable with the most important prognostic value, even if the occurrence of seizures themselves, both in animal models and in human newborns,[13–16] appears to influence the long term outcome.[4,5,17] Furthermore, the presence of seizures in preterm infants seems to carry negative prognostic implications but, to date, this topic is still under-reported.

The aim of our study is to describe the main characteristics of neonatal seizures in a cohort of preterm newborns and to identify the neonatal factors that predict the unfavorable outcome.

2. Methods

We collected a sample of 76 preterm infants, among the154 newborns with v-EEG confirmed neonatal seizures consecutively admitted to the neonatal intensive care unit (NICU) of Parma University Hospital between January 1999 and December 2012. All preterm babies at high risk of seizures, because of predisposing factors such as birth asphyxia, sepsis, meningitis, metabolic disorders, evidence of brain malformations, IVH/IVH aggravation or periventricular leukomalacia (PVL) on brain ultrasounds, or in the presence of clinical signs suggestive of seizures underwent serial v-EEG recordings during the neonatal period. Inclusion criteria for the neonatal seizures group included v-EEG-confirmed neonatal seizures and the availability of more than one EEG recording during the NICU stay.

All the subjects had more than one cerebral ultrasound (CUS) examination performed up to term age and at least one computed tomography and/or cerebral MRI within the first year of life. Follow-up was at least 12 months in the survivors.

The following variables were collected in connection with the presence of seizures and mortality: natural childbirth or cesarean section, gender, gestational age, birth weight, Apgar score at the first, fifth min, and when available at the tenth min. Clinical history of pregnancy and perinatal events were collected at the time of hospital admission. Gestational age was measured in weeks and evaluated according to the day of the last menstrual cycle and/or to the chronological age assessed by ultrasound examination performed before the 20th week of gestation. Based on gestational age, our sample was divided into 2 subgroups: 1) between 30 and 36 weeks, and 2) $\leq$ 29 weeks. Birth weight was ranked in 4 categories: neonates weighing $\geq$2500 g, between 1500 and 2499 g, between 1000 and 1499 g, and <1000 g. Apgar scores at the first and fifth min were ranked as follows: below or equal to three; between four and seven and equal to or above eight. Perinatal disorders usually associated with prematurity were also recorded. Perinatal asphyxia was defined in the presence of at least three of the following conditions: intrapartum distress, as indicated by fetal bradycardia with a heart-rate of less than 100 beats per minute, late decelerations or absence of heart-rate variability; thick, meconium-stained amniotic fluid; an Apgar score $\leq$5 at 5 min; a need for resuscitation for more than 1 min with positive-pressure ventilation and oxygen immediately after birth; arterial-blood pH value $\leq$ 7.10 or a base deficit of at least 14 mmol per liter within the first hour after birth.[18]

The first neurologic examination findings, evaluated according to gestational age, were classified into three categories (modified from Legido 1991): 1) normal or mildly abnormal; 2) moderately abnormal, such as hypotonia/hypertonia, decreased muscle active movements, lethargy; and 3) severely abnormal, such as flaccid, inactive and coma.[19] Time of seizure onset was divided into before or after the first 48 h of life. Based on seizure semiology, patients were classified as having one or multiple seizure types. The occurrence of neonatal status epilepticus was also coded as a variable.

Neonatal seizures were classified according to Volpe's classification modified by Lombroso[20] and, according to the new proposed classification of the International League Against Epilepsy,[21] had to be associated with electrographic changes. Clinical seizures without EEG correlates were not considered. Furthermore, according to the new classification,[21] spasms were added as a type of seizures.

2.1. *Electrophysiological and neuroimaging assessment*

Polygraphic v-EEG methods and criteria applied to assess EEG background activity were reported previously.[22,23] Polygraphic v-EEGs were obtained at the bedside in the NICU. Depending on the infant's head size, electrodes were applied according to the International 10–20 System modified for newborns. Electrocardiogram, lateral eye movements, surface electromyographic activity and abdominal respiration were the other most frequently monitored physiological variables; an EEG technician was present throughout the entire recording. The recordings continued until a complete cycle of wakefulness, quiet, and active sleep were obtained. However, when the state changes were not clearly distinguishable, the recording continued for at least 60 min. Standardized age-dependent criteria[24] were applied to assess EEG background activity, which was scored as: I) normal; II) mildly abnormal: excess sharp activity, absence or decreased frequency of normal patterns, excessively long low-voltage periods or overall slightly decreased voltage; III) moderately abnormal: asymmetries in