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Orginal article

Neonatal status epilepticus: Differences between preterm and term newborns

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ABSTRACT

Background: Despite the many studies on neonatal seizures, neonatal status epilepticus (NSE) remains a controversial entity, with no general consensus about its definition. We report the characteristics of newborns with NSE in order to assess whether they showed homogeneous features or displayed clinical and/or instrumental differences depending on gestational age (GA). Preterm and term neonates were compared and risk factors for adverse outcome evaluated.

Methods: From 154 newborns with video-EEG confirmed neonatal seizures admitted to the NICU of Parma University Hospital between January 1999 and December 2012, we collected a cohort of 47 newborns (19 preterm, 28 full-term) with NSE. NSE was defined as continuous seizure activity for at least 30 min or recurrent seizures lasting a total of 30 min without definite return to the baseline neurologic condition between seizures. Outcome was assessed at least at one year. We applied the χ^2 test to compare nominal data, and multivariate logistic regression analysis to determine independent risk factors for adverse outcome.

Results: Only Apgar scores and neurologic examination ($p \leq .02$) were different between the groups. None of the preterm newborns had a favourable outcome compared to 25% of the full-term ones ($p = .032$). Moreover, 52.6% of preterm neonates died compared to 17.8% of the full-term newborns ($p = .01$; OR = 5.11). The only variable related to outcome was Apgar score at 5 min ($p = .02$).

Conclusion: Newborns with NSE represented a quite homogeneous group regardless of the GA. Outcome was unfavourable in most of the subjects; however adverse outcome and death were more represented in preterm newborns.

Abbreviations: GA, gestational age; IVH, intraventricular hemorrhage; NS, neonatal seizures; NSE, neonatal status epilepticus; PVL, periventricular leukomalacia; US, cerebral ultrasound; v-EEG, video-electroencephalogram.

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1. Introduction

Neonatal status epilepticus (NSE) is still a controversial entity, for which a specific and worldwide accepted definition does not exist. However, different definitions,[1–7] mostly arbitrary and based on temporal criteria, have been applied to define this entity and several studies showed a wide variety of NSE percentage in newborns with neonatal seizures (NS), ranging from 8% up to 43%.[4,8] This variability is probably due to the different definitions and inclusion criteria used to diagnose NSE. In older ages, status epilepticus was usually defined as a continuous seizure activity lasting for at least 30 min, or recurrent seizures lasting 30 min or more from which the patient does not regain consciousness.[9] A more operational definition was proposed for generalized, convulsive status epilepticus in adults and children, being a continuous seizure or two or more discrete seizures between which there is incomplete recovery of consciousness for ≥5 min.[10] However, it is still debated if these definitions are applicable to newborns.[11–17] Beyond the adopted definition, it seems that the effects of prolonged seizures on the developing brain lead to a poor outcome.[1,2,5,18–20] This study, focused on newborns with status epilepticus, evaluates the differences between preterm and full-term newborns and also the risk factors for an adverse outcome have been analysed.

2. Methods

We selected 47 newborns with NSE out of 154 newborns with video-EEG (v-EEG) confirmed NS, selected among the 5100 neonates consecutively admitted to the NICU of Parma University Hospital, between January 1999 and December 2012. NSE was defined as continuous seizure activity for at least 30 min or recurrent seizures lasting a total of ≥30 min without definite return to the baseline neurologic condition of the newborn between seizures, in any 1-h period (hourly seizure burden range: ≥ 50%–100%).[9,19,21] The following inclusion criteria were applied: 1) v-EEG confirmed NS; 2) more than one cerebral ultrasound (US) examination performed up to term age and at least one computed tomography and/or cerebral MRI within the first year of life; 3) a follow-up of at least 12 months. All newborns at high risk of seizures due to predisposing factors such as birth asphyxia, sepsis, meningitis, metabolic disorders, brain malformations, intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) on brain US scans, or in the presence of clinical signs suggestive of seizures, underwent serial EEGs during the neonatal period. NS were classified according to Volpe's classification modified by Lombroso[22] and had to be associated with electrographic changes. Polygraphic v-EEG were obtained at the bedside and, depending on infants' head size, 21 or 10 cerebral electrodes were applied according to the 10–20 International System. Electrocardiogram, lateral eye movements, chin electromyographic activity, and abdominal respiration were the other physiologic variables most frequently monitored. The recordings continued until a complete cycle of awake, quiet, and active sleep were captured, or, if these were not clearly distinguishable, the recording continued for at least 60 min and could be further prolonged on the basis of seizures course and clinical needs. Moreover, almost all the subjects with NSE underwent at least one follow-up EEG recording during the subsequent 24 h from the first one. Standardized age-dependent criteria were applied to assess EEG background activity.[23] The study was conducted on data from a NS database, continuation of a database whose clinical features have been previously described.[19,24] Outcome was assessed at discharge, 3, 6, 9, 12 months and afterwards every six months with a follow-up from a minimum of 12 months to a maximum of 13 years according to clinical conditions. Neuromotor assessment was based on clinical criteria,[25,26] and general development was assessed using the Griffiths' Mental Developmental Scale and, after 2007, the Bayley Scales of Infant and Toddler Development II.[27,28] The neurodevelopmental outcome was classified as favourable or adverse. A favourable outcome was defined as normal neurologic development or mild muscle tone and reflexes abnormalities and isolated speech delay, whereas adverse outcome was identified as involvement resulting in death, cerebral palsy, developmental delay, epilepsy, blindness, or deafness.

2.1. Statistical analysis

Nominal data were analysed using the χ^2 test, and if necessary, the Fisher exact test for two-by-two comparisons. A univariate logistic regression model to determine which independent variable(s) were related to outcome was used. Variables with a p value < .05 on univariate analysis were included in a multiple logistic regression analysis. The multiple logistic regression analysis was performed to detect independent risk factors for adverse outcome. For these purposes, adverse outcome and death were considered as a single group. In all instances, a p value of less than .05 was considered to be significant. Statistical analysis was performed using the Statistical Package for the Social Sciences (Version 20.0; IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp, 2011).[29] For the statistical analysis, the first neurologic examination findings, evaluated according to GA, were grouped in three categories (modified from Legido 1991[30]): 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. EEG findings were grouped into two categories: 1) normal or mildly abnormal (normal or excess sharp activity, absence or decreased frequency of normal patterns, excessively long low-voltage periods or overall slightly decreased voltage); and 2) moderately or severely abnormal (asymmetries in voltage or frequencies, asynchrony for age, or isoelectric/low-voltage invariant activity, burst-suppression pattern, permanent discontinuous activity). US findings were grouped into three categories: I) normal; II) IVH of degree I or II, transient periventricular echodensities; and III) IVH of degree III or IV, intraparenchymal hemorrhage, PVL, brain malformations. Aetiologies were grouped in the following three categories: hypoxic–ischaemic encephalopathy, cerebral hemorrhage, and others (congenital metabolic and transient metabolic disorders, infectious diseases, brain malformations, unknown causes).