Neurodevelopmental outcome predictors of term newborns with neonatal seizures

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Introduction. The concrete burden of neonatal seizures in neurodevelopmental outcome of term newborns is still unknown in literature. The aim of this study was to describe prognostic predictors in neonatal seizures.

Subjects and methods. Observational prospective study of term neonates with clinical seizures from a tertiary center (2009-2018). Adverse outcome was determined as death, global developmental delay, cerebral palsy or epilepsy. Perinatal characteristics, etiology, electrographic features, neuroimaging and antiepileptic treatment were analyzed in a logistic regression model.

Results. A total of 102 newborns were included (52 infants with normal outcome). Twelve fatalities were registered. In the survival group, 38 children had an adverse outcome (28 global developmental delay, 27 cerebral palsy, 21 epilepsy). From the prognostic variables identified in univariate analysis, perinatal complications, seizure onset in the first day of life, moderate to severe abnormal background activity, abnormal amplitude-integrated EEG pattern, and treatment response remained independently associated with adverse outcome after a logistic regression model.

Conclusions. There is conflicting data about surrogate markers in neonatal seizures. Aside from confirming the predictive value of previously described variables, we observed that amplitude-integrated EEG monitoring is a forthcoming prognostic tool. Future approaches may include a wider use of amplitude-integrated EEG monitoring, being crucial for timely seizure identification and prompt treatment.

Key words. Amplitude-integrated EEG. Convulsions. Neonatal. Newborn. Outcome. Seizures. Term.

Introduction

Epileptic seizures represent one of the commonest manifestations of acute neurologic disturbances during the neonatal period [1]. The concrete seizure burden responsible for cerebral damage is still unknown in literature, having implications in neonatal prognostication and treatment. Distinguishing between etiologic and seizure induced effects on neurodevelopment is challenging and has mostly limited clinical research on neonatal seizures.

The aims of this study were to evaluate the variables associated with adverse neurological outcome in term neonates with seizures.

Subjects and methods

We conducted an observational prospective study in a cohort of term newborns (i.e., ≥ 37 weeks gestation), with clinically evident seizures during the neonatal period (i.e., within the first 28 days of life), who were admitted in the Neonatal Intensive Care Unit (NICU) of a single tertiary level hospital, from January 2009 to December 2018. Only patients with a minimum of two years of neurological follow-up were included. Patients who died as consequence of the neurologic disorder were included if all required data was available and if they had at least one year of follow-up. Medical records were reviewed and data was collected regarding clinicodemographic characteristics, etiology, electroclinical features, neuroimaging, antiepileptic treatment and neurological outcome.

The diagnosis of neonatal seizures was concluded by a pediatric neurology consultant based on clinical observation or description. Seizures were classified according to Volpe's classification modified by Lombrose [2], as subtle, focal clonic, multifocal clonic, focal tonic, generalized tonic and myoclonic phenomena. In patients presenting with more than one seizure type, the most representative manifestation was considered. The time of seizure onset was classified as early if occurring during the first 24 hours of life. In all patients, seizure investigation required a monitoring video-EEG

study within 24 hours of the paroxysmal event and a minimum record duration of 24 hours. Perinatal complications included fetal distress, complicated (prolonged/precipitated) labor and resuscitation maneuvers. The primary etiology of seizures was established by the pediatric neurologist, according to clinical history, neuroimaging (cranial ultrasonography and brain MRI) and laboratory investigation (including blood and cord pH, when available). Patients in whom no etiology was determined through proper investigation were classified as unknown.

EEG recordings were visually analyzed by an experient pediatric neurophysiologist. Conventional EEG (cEEG) was classified with respect to the presence of interictal/ictal epileptiform discharges and abnormal background activity. According to gestational age, the assessment of background activity was based on the voltage depression and asymmetries, being further classified as normal/mild or moderate/severe abnormality. Whenever available, amplitude-integrated EEG (aEEG) was also performed and classification of a normal/abnormal pattern was made by a neonatologist or pediatric neurologist. The most altered EEG study was used for the analysis. Neuroimaging studies (transcranial ultrasonography and brain MRI) were considered abnormal if there was evidence of cerebral lesions, malformations or other remarks. The use of antiepileptic drugs as acute or maintenance therapy was also assessed.

In our center, clinical surveillance of patients with neonatal seizures is made by a pediatric neurologist. The neurological outcome obtained in the last follow-up visit was included in the analysis and classified as adverse if one or more of the following were present:

- Cerebral palsy, determined according to the accepted definition as a static, non-progressive and permanent condition of movement and motor impairment [3].
- Global developmental delay, determined according to the definition as a significant delay in two or more developmental domains [4].
- Epilepsy, determined according to International League Against Epilepsy definition guidelines [5].
- Death occurring as consequence of the neurological sequelae.

All variables were analyzed in regard to the development of a normal or adverse neurological outcome. Statistical analysis was performed using SPSS v. 24 software. Summary statistics were reported as mean ± standard deviation. Chi-square test and binary logistic regressions were used to assess the association between dichotomous adverse outcome (yes/no) with other variables and combinations. The level of significance adopted was $\alpha = 0.05$.

Results

Demographic and clinical data

During the study period, a total of 102 patients –56% (n = 57) males and 44% (n = 45) females– were included, of whom 51% (n = 52) presented a normal outcome. In the adverse outcome group (n = 50), 12 case fatalities were registered with a mean age of 33 ± 5.8 months (range: 0-72). Thirty-eight children survived with one or more neurological impairment. The most frequent adverse outcome was global developmental delay (n = 28), followed secondly by cerebral palsy (n = 27), from which quadriplegic type was the most prevalent (n = 9). Seventeen children developed post-natal epilepsy plus cerebral palsy and 19 developed post-natal epilepsy plus global developmental delay. Mean follow-up age was 4.7 ± 1.3 years (range: 2-5) and mean duration of NICU admission was 8.1 ± 10.4 days (range: 2-55).

Perinatal features

Mean mother age was 28.9 ± 6.4 years (range: 24-37). Sixty-nine patients were born from vaginal delivery. Mean gestation age was 38.6 ± 2.5 weeks (range: 37-41) and mean birth weight was 3211 ± 535 g (range: 1488-4700). Perinatal complications occurred in 38 patients: fetal distress in cardiotocography (n = 20), complicated delivery (n = 22), and need for resuscitation (n = 9). The mean Apgar score at 5th minute was 8.2 ±1 (range: 0-10). In a univariate analysis, only the occurrence of perinatal complications was significantly associated with an adverse neurological outcome (p = 0.04).

Etiology

Hypoxic-ischemic encephalopathy was the most common seizure etiology (57%; n = 58), followed by perinatal ischemic stroke (16%; n = 16) and intracranial hemorrhage (12%; n = 12). In a univariate analysis, a significant association was observed between hypoxic-ischemic encephalopathy and adverse outcome (p = 0.03), when compared to other etiologies. Case fatalities were also more frequent in the former (n = 11).

Seizure characteristics

The age of seizure onset ranged from < 24 hours to 9 days of life. Early seizure onset (i.e., occurring in the first day of life) occurred in 39% (n = 40) neonates, of whom 27% (n = 28) patients had an unfavorable outcome. The most common seizure types were focal clonic (28%), followed by multifocal clonic (19%), generalized tonic (19%) and focal tonic (18%). In a univariate analysis, early seizure onset was significantly associated with adverse neurological outcome (p = 0.002). No statistical difference was observed regarding seizure types, which was further confirmed by the analysis of focal clonic and non-clonic manifestations (p > 0.20).

EEG

A total of 82% (n = 83) newborns had an abnormal cEEG. Moderate to severe abnormal background activity was found in 29% (n = 30) neonates and epileptiform activity in 77% (n = 79). In a univariate analysis, only moderate to severe abnormal background was significantly associated with worse prognosis (p = 0.001), as no difference was found regarding epileptiform activity (p = 0.15). In 91 patients, aEEG monitoring was performed in addition to cEEG and an abnormal pattern was found in 62% patients. In univariate analysis, an abnormal aEEG pattern was also significantly associated with adverse neurological outcome (p = 0.05).

Neuroimaging

Both neuroimaging studies, brain MRI and transfontanelar ultrasound, were performed in all patients. In the adverse outcome group, 54% (n = 22) and 63% (n = 45) newborns had an abnormal result of MRI and transfontanelar ultrasonography, respectively. In a univariate analysis, cranial ultrasonography was significantly associated with adverse neurological outcome (p = 0.03) and no difference was observed regarding brain MRI results (p > 0.20).

Treatment

Only two patients did not require antiepileptic treatment. During the neonatal period, seizures were controlled in 57 newborns with phenobarbital on monotherapy. In 43 newborns, one or more antiepileptic drugs were necessary in addition to phenobarbital: midazolam (n = 19), phenytoin (n = 16), clonazepam (n = 4), lidocaine (n = 2), and others (n = 2). Forty-six patients were discharged on antiepileptic treatment. In a univariate analysis, the requirement of add-on antiepileptic drugs to phenobarbital was significantly associated with adverse outcome (p = 0.002).

Neurological outcome

From the potential predictors of outcome identified in the univariate analysis, the variables perinatal complications, early seizure onset, moderate to severe abnormal background activity, abnormal aEEG pattern, and administration of add-on antiepileptic drugs to phenobarbital remained independently associated with adverse outcome after a logistic regression model (Table). All patients enrolled in the study had available data for these variables. Of note, electrographic features of moderate to severe background abnormality was six times more likely associated with unfavorable outcome (odds ratio = 6.25; 95% confidence interval: 1.89-18.3; p = 0.004) than normal or mild background slowing. In addition, in our study we equally found that the identification of an abnormal aEEG pattern was three times more likely to be associated with adverse neurological outcome (odds ratio = 2.87; 95% confidence interval: 2.3-14.4; p = 0.03).

Discussion

Neonatal seizures are the most frequent manifestation of acute disturbances occurring in the developing brain [2]. Although the mortality of newborns with seizures has significantly declined in the last decade due to improved perinatal care [6,7], neonatal seizures still pose significant impact on long-term morbidity, including neurodevelopmental disorders [8-10] and epilepsy [9,11-13]. Since earlier studies, the most important outcome predictors have been associated with the underlying pathology and severity of brain injury, rather than the consequence of seizures per se [6,14,15]. It has been generally accepted that subsequent neurological impairments are mainly determined by seizure etiology, largely represented by hypoxic-ischemic encephalopathy or intrapartum asphyxia in full term neonates [16]. However, the prognostic value for other variables, such as perinatal characteristics, electroclinical features and treatment efficacy has not been consensual. Significant variation in gestational age, underlying brain insults, as well as seizure detection and electrographic analysis, accounts for such discrepant results and has limited

Table. Association of statistically significant independent variables and neurological outcome.

		Total (*n*)	Normal outcome		Adverse outcome		Univariate analysis	Multivariate analysis	
			n	%	*n*	%	*p*	*Odds ratio* (95% CI)	*p*
Perinatal complications	Absent	64	43	67	21	33	0.04	6.29 (3.1-12.9)	0.03
	Present	38	9	24	29	76			
Seizure onset	< 24 h	40	12	30	28	70	0.002	3.91 (2.14-22.8)	0.05
	> 24 h	62	40	64	22	36			
Conventional EEG (moderate to severe abnormal background)	Yes	30	23	77	7	3	0.001	6.25 (1.89-18.3)	0.004
	No	72	29	40	43	60			
Amplitude-integrated EEG	Normal	28	25	89	3	11	0.05	2.87 (2.3-14.4)	0.03
	Abnormal	63	21	33	42	67			
Anticonvulsant treatment	Phenobarbital only	57	39	68	18	32	0.002	6.72 (1.1-25.7)	0.001
	Additional AED required	43	11	25	32	75			

AED: additional antiepileptic drugs; EEG: electroencephalography; 95% CI: 95% confidence interval.

an homogenous research on neonatal seizures [17]. Despite such restraints, there is converging evidence that seizures independently of etiology [18] and certain electrographic patterns represent crucial prognostic markers [19].

In this study, we assessed the predictive value of a gamut of variables potentially associated with outcome. There are major differences between term and preterm infants in what concerns etiology, seizure type and morbidity [20,21]. Most previous studies have included both term and preterm newborns, which may be responsible in some degree for the variability observed in prognosis prediction. Moreover, several studies concluded that premature neonates with seizures have higher probability of an adverse neurological outcome [9,11,20,22]. Evidence on outcome in the particular case of term infants with seizures is scant and has been only evaluated in two previous studies [8,23]. Therefore, we aimed to include a homogenous population of exclusively term neonates. Pisani et al scoring system [24], which included preterm and term infants, identified six independent risk factors for adverse neurological outcome: birth weight, Apgar score at 1 min, neurological examination, cerebral ultrasound, efficacy of anticonvulsant therapy, and status epilepticus. In order to overcome population study differences, Garfinkle et al developed a prognostic scoring system exclusively for term infants and identified five independent risk factors: type of delivery, seizure onset, seizure type, EEG background findings, and etiology. Ronen et al have further suggested that poor prognostic markers are more reliable when combining clinical, electrographic and neuroimaging results than using clinical or EEG criteria alone [9].

An increased risk of cerebral palsy, global developmental delay and post-natal epilepsy has been long associated with neonatal seizures. We classified these disabilities as adverse outcome because they often coexist [21]. Our cohort showed a 49% prevalence of unfavorable outcome, which is concordant with others observations whose definition of adverse prognosis was similar to ours [9,23,25]. The burden of epilepsy can be interpreted as a marker of brain injury severity, based on the fact that infants with epilepsy are equally affected by cerebral palsy and intellectual disability [26]. Nevertheless, this conclusion may be too simplistic, inasmuch as neonatal seizures may also play a synergistic effect in cerebral damage. The rate of post-natal epilepsy ranges from 18% to 25% according to hos-

pital-based series, which is in line with our results. However, the incidence in the setting of intensive care units may be higher compared to population-based series, thus reflecting a possible selection bias [18,27,28].

As previously reported in other studies, we confirmed that hypoxic-ischemic encephalopathy was the most frequent etiology [16,29], occurring in 57% of cases. Albeit associated with worse prognosis in the univariate analysis, we did not find statistical significance after a logistic regression model. Our findings are in keeping with other case-series [23], which suggests that the extent of hypoxic brain injury itself accounts for the impaired neurodevelopment, rather than the underlying pathology. This is further supported by the absence of an association found between outcome and MRI or cranial ultrasonography abnormal results, as it did not specifically assess the extension of cerebral injury. Regarding variables pertaining to perinatal conditions, only perinatal complications (fetal distress, complicated delivery, need for resuscitation) were independently associated with adverse outcome. Preterm gestational age and low birth weight have been extensively reported in relation to prognosis [21,30]. In our study, these variables were not related with adverse prognosis since we exclusively evaluated term newborns. We neither found an association with the type of delivery, confirming previous remarks that neonatal seizures morbidity is not related with cesarean section [22,31].

Seizure type was not associated with adverse outcome. A correlation between focal clonic seizures and better prognosis was initially described in large case-series [23,32]. However, reproduction of such results has not been consistent and further studies did not conclude an association between semiology and long-term outcome [33,34]. On the other hand, we found that seizure onset in the first day of life and treatment refractoriness were strong predictors. The prognostic value for both variables are in keeping with other descriptions [21]. In our cohort, we found that neonates requiring additional antiepileptic drugs to phenobarbital were seven times more likely and neonates with early seizure onset were four times more likely to have unfavorable prognosis.

EEG abnormalities in neonatal seizures are well documented prognostic markers [35,36]. Interictal epileptic activity has been associated with unfavorable outcome, in addition to the limited availability of ictal recordings. However, numerous studies have demonstrated that moderate to severe abnormal background is more significantly related with unfavorable prognosis than epileptiform discharges [8, 23,35]. For this reason, we analyzed cEEG specifically concerning either the presence of an abnormal background or epileptiform activity. Our results showed that moderate to severe abnormal background is an independent predictor of adverse outcome and we found no difference regarding the presence of epileptiform activity. This observation corroborates the previous notion that epileptiform discharges do not necessarily correlate with the extension of cerebral injury.

In addition to cEEG, we assessed the use of aEEG as a prognostic tool and observed that an abnormal aEEG pattern was also independently associated with outcome. In neonatal seizures, evidence about the utility of aEEG in predicting prognosis is still very scarce in literature. It is generally agreed that cEEG has a higher sensibility and specificity in detecting seizures than aEEG [37], therefore our study only included newborns in whom aEEG was performed in addition to monitoring video-EEG. One previous study authored by Zhang et al also substantiated an association between abnormal patterns detected on aEEG and long-term adverse outcome [38].

Our study has methodological limitations. Seizures were diagnosed based on clinical description by an experient pediatric neurologist, thus reproducing a real NICU daily setting in which EEG monitoring is not immediately available. This clinical approach implied a subjective variability in seizure detection. In order to overcome such issue, gold standard video-EEG monitoring was required to assure a higher probability of event recording. In case no event was further recorded, the clinical observation would still prevail. Another limitation of our study was the dichotomic assessment of brain MRI and transcranial ultrasonography as normal or abnormal results. We speculate that specifically evaluating the severity of brain lesions would have been useful, for instance in the case of basal ganglia and thalamic lesions in hypoxic-ischemic encephalopathy.

There is a wide range of data in literature about surrogate markers of prognosis in neonatal seizures. In our study, the multivariate regression analyses denoted that independent variables for adverse neurological outcome were perinatal complications, early seizure onset, treatment efficacy, moderate to severe background abnormality on cEEG, and an abnormal aEEG pattern. In the present study, the advantage of using aEEG to evaluate neonatal seizures is noteworthy, as abnormal findings are readily detectable and have significant prognostic implications.

In conclusion, to date neonatal seizures detection and classification, underlying brain pathology and real impact on long-term prognosis are still controversial. Aside from confirming the predictive value of variables described in previous studies, we have observed that aEEG monitoring represents a forthcoming prognostic tool. Future approaches will be urged by the wider use of long-term aEEG monitoring, which is more promptly available in the setting of intensive care units than monitoring video-EEG. These findings are crucial for timely seizure identification and prompt treatment.

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Predictores pronósticos de desarrollo neurológico en recién nacidos a término con crisis neonatales

Introducción. El peso específico de las crisis neonatales en el pronóstico neurológico de recién nacidos a término no se conoce bien, por lo que el objetivo del estudio era describir predictores pronósticos en crisis neonatales.

Sujetos y métodos. Estudio observacional prospectivo de recién nacidos a término con crisis clínicas en un centro terciario (2009-2018). Pronóstico adverso se definió como muerte, retraso global del desarrollo, parálisis cerebral o epilepsia. Se analizaron las características perinatales, la etiología, los hallazgos electroencefalográficos, la neuroimagen y los tratamientos antiepilépticos siguiendo un modelo de regresión logística.

Resultados. Se incluyó a un total de 102 recién nacidos (52 de los cuales tenían desarrollo normal). Se registraron 12 fallecimientos. En el grupo de supervivientes, 38 niños tuvieron un pronóstico desfavorable (28 con retraso global del desarrollo, 27 con parálisis cerebral, 21 con epilepsia). De las variables pronósticas identificadas en el análisis univariante, las complicaciones perinatales, el inicio de las crisis en el primer día de vida, la actividad basal anormal moderada a grave, un patrón anormal en el electroencefalograma de amplitud integrada y la respuesta al tratamiento continuaron mostrándose como independientemente asociadas a pronóstico adverso después de aplicar un modelo de regresión logística.

Conclusiones. Existen datos contradictorios sobre marcadores subrogados en crisis neonatales. Aparte de confirmar el valor predictivo de variables previamente descritas, se halló que la monitorización con electroencefalograma de amplitud integrada constituye una prometedora herramienta diagnóstica. En el futuro, se debería extender su utilización en el abordaje de estos pacientes, lo que sería de vital importancia para un diagnóstico y un tratamiento precoces.

Palabras clave. Convulsiones. Crisis. Electroencefalograma de amplitud integrada. Neonatal. Neonatos nacidos a término. Pronóstico. Recién nacido.