

COMPARATIVE CLINICAL STUDY OF PRETERM AND FULL-TERM NEWBORN NEONATAL SEIZURES

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ABSTRACT - Objective: To compare the characteristics of neonatal seizures between preterm and full-term infants in intensive care unit. **Method:** A prospective study was developed with 104 high-risk newborn, 30 preterm and 74 full-term infants, with clinical seizures. The dependent variable was gestational age. **Statistical analyses:** Fisher's exact test, odds-ratio and Mann Whitney U test. **Results:** There were significant differences ($p < 0.05$): i) premature neonates develop neonatal seizures later, probably related to the etiologies of the seizures; ii) etiologically, there is a predominance of peri-intraventricular hemorrhage in preterm and of asphyxia in full term neonates; iii) clonic seizures are most frequent in preterm and subtle seizures in full term neonates. **Conclusion:** Although the study had a clinical basis, it was possible to identify differences when the dependent variable was gestational age.

KEY WORDS: neonatal seizures, gestational age, comparative study, neonate, preterm infant, full-term infant.

Estudo clínico comparativo das convulsões neonatais entre recém nascidos pretermo e termo

RESUMO - Objetivo: Comparar as características das convulsões neonatais entre recém nascidos prematuros e de termo internados em Unidades de Terapia Intensiva. **Método:** O estudo prospectivo neonatal avaliou 104 recém nascidos, 30 neonatos prematuros e 74 de termo, com crises convulsivas. As crises foram diagnosticadas pelas características clínicas. A variável dependente foi a idade gestacional. Na análise estatística utilizamos o teste exato de Fisher, odds ratio e o teste U de Mann Whitney. **Resultados:** Observamos diferenças estatísticas significantes ($p < 0,05$): i) os neonatos prematuros manifestaram crises convulsivas mais tardiamente, provavelmente, relacionadas à etiologia; ii) observamos predomínio da hemorragia peri-intraventricular nos neonatos prematuros e a asfíxia nos recém nascidos de termo; iii) as crises clônicas foram mais frequentes nos neonatos prematuros e as sutis nos neonatos de termo. **Conclusão:** Embora o estudo tenha uma base clínica, foi possível identificar diferenças quando a variável dependente foi idade gestacional.

PALAVRAS-CHAVE: convulsões neonatais, idade gestacional, estudo comparativo, neonatos pretermo, neonatos de termo.

The occurrence of any manifestation of neonatal seizures (NS) indicates a primary or secondary dysfunction of the central nervous system¹⁻³. Thus, determination of etiology is critical, because it gives the opportunity to treat and to make a meaningful statement about the prognosis³⁻⁵. Nowadays, NS is defined by video-electroencephalographic monitoring, by clinical observation associated to ictal or interictal electroencephalogram (EEG), by electrographic discharge without associated clinical manifestation or by neonatal polysomnography^{4,6-12}. However, in clinical practice

at the pediatric or neonatal intensive care units (ICU), in developing countries where synchronized video-EEG monitoring is practically non-existent, clinical observation becomes the key to the diagnosis³.

On the other hand, we know that seizure phenomenon in preterm infant (PN) is less organized than it is in full-term infant (FT)^{3,13,14}. So, when we compare the clinical diagnosis of NS having gestational age as dependent variable, is the clinical profile different between the preterm and full-term infants?

The objective of this study was to determine the

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NS differences between PT and FT infants who were admitted to neonatal intensive care or pediatric ICU, based on clinical observations.

METHOD

We performed a prospective study from August 1st, 2001 to July 31st, 2002 in 9 ICU in Natal, Brazil. We selected all neonates that presented seizures during ICU stay. Preparatory educational sessions were held in order to standardize and improve the quality of observation and identification of NS. Semiology of seizures as well as stimulation and restraint maneuvers were also discussed. These sessions included teams of neonatologists, intensive care pediatricians and nursing staff. A standard protocol of studying NS was developed jointly with the aforementioned teams. Accordingly, NS were defined as a paroxysmal phenomenon, required to have at least one of the following clinical manifestations: changes in behavior, stereotyped or periodic motor activities or autonomic dysfunctions³. We used the classification proposed by Volpe¹⁵ featuring four essential types: subtle, clonic, myoclonic, and tonic.

Gestational age was estimated based on the date of the last menstrual period, from obstetric ultrasonography or from a clinical estimates (Capurro's method or New Ballard Score). The newborn were determined as preterm when the gestational age was less than 37 weeks and full-term from 37-43 weeks.

The inclusion criteria were as follows: 1) detailed and unequivocal description of NS by the team; 2) seizures unresponsive to restraining maneuvers and unprovoked by stimulation and 3) occurrence of the first seizure up to 28 days old.

The exclusion criteria were: 1) uncertain clinical manifestations, 2) admission to ICU with NS diagnosis but not presenting any such episode during the stay, 3) those who had the first seizure after 28 days of life and 4) unidentified gestational age.

The dependent variable was gestational age; the quantitative independent variables were maternal age, number of gestations, maternal parity, Apgar at 1 and 5 minutes and the age at the first seizure. Independent category variables were: sex, type of delivery, depressed Apgar (0 to 6 scores), severe depressed Apgar (0 to 3 scores), seizures type, seizure recurrence, presumed etiologies and mortality. Recurrence were defined when seizure repeats 24 hours after to get controlled. Deliveries were classified as vaginal and operative (caesarean section and forceps). The seizure's etiology was defined based on ICU's guidelines. Neuro-ultrasonography scan were obtained, when possible, utilizing a GE Logiq Pro 400 machine.

The data were recorded in Epi-Info 6.0. The statistical analysis was performed by SPSS (Statistical Package for Social Science for Windows). Significance was obtained by Fisher's exact test. Odds ratio was analyzed when the independent variables were dichotomous. Mann Whitney U test were performed for quantitative variables. The significance was considered when p value <0.05.

RESULTS

During the period of the study were admitted to the 9 ICU 1646 neonates, of these 1376 (83.3%) were in public hospitals, and 270 (16.4%) in private hospitals. We observed NS in 114 (6.9%) of the newborn infant, of which 103 (90.0%) were in public hospitals and 11 (10.0%) in private institutions. In accordance with inclusion and exclusion criteria we selected 30 (28.8%) PN and 74 (71.2%) FT.

The average birth weight of PN was 1676.6g, standard deviation 794.3g; median 1676.4g; mode 900g and range from 790 to 3650g. In FT the average was 3167.9g, standard deviation 559.2g; median 3155g; mode 3000g and range from 1605 to 4340g. The average gestational age of PN was 31.5 weeks; standard deviation 3.8 weeks; median 32 weeks; mode 31 weeks; and range from 23 to 36 weeks. The average of gestational age of FT was 39.6 weeks; standard deviation of 1.4 weeks; median 40 weeks; mode 39 weeks and range from 37 to 43 weeks.

In Table 1 we demonstrated median, well as dispersion and variability of the quantitative independent variables. The Mann Whitney U test (Table 1) showed a significant statistical difference for the age of NS onset, later in PN (p=0.000).

Table 2 shows the data relative to the categorical variables. The male sex predominated in both full-term and preterm groups. In 1 FT it was not possible to determine the sex (ambiguous genitalia). General mortality was 21.15% (n=22). Comparing the two groups, there was a mortality rate of 36.6% (n=11) in PN and 14.8% (n=11) in the FT, with statistical significance (p=0.014). Depressed Apgar at 1 minute was less common in PN and the difference was statistically significant (p=0.006).

Table 3 represents data referent to NS classification. Subtle seizures predominated in FT (72.9%) and clonic seizures (50%) in PN. Analysis showed a significant statistical difference for subtle seizures being less frequent in PN (p=0.000) and for clonic seizures being more frequent in PN (p=0.000). In 28 (27%) newborn infants, 8 (26.6%) premature and 20 (27.0%) full-term, we observed more than one type of NS. Recurrence of NS occurred in 20 (19.3%) of the neonates. In full-term neonates there was a recurrence in 16 (21.6%) and in the premature in 4 (13.3%).

Neuro-ultrasonography scan were performed on 58 (55.7%) of the neonates and 17 (29.0%) of these were found to be abnormal. The findings were abnormal in 9 (30.0%) of PN and in 8 (10.8%) of FT.

Table 4 gives information about probable of NS etiologies. The PN presented with less HIE than the

Table 1. Median, dispersion and variability of quantitative variables in 30 preterm and 74 full-term infants with neonatal seizures.

Quantitative variable	Gestational age	n	Median	ID	Minimum	Maximum	p value
Apgar at 1 minute	Preterm	29	5.0	3.0	1	9	0.373
	Full-term	65	4.0	5.0	0	9	
Apgar at 5 minutes	Preterm	29	7.0	3.0	3	10	0.823
	Full-term	65	7.0	4.0	1	10	
Maternal age (years)	Preterm	29	23.0	11.0	18	38	0.807
	Full-term	72	24.5	13.5	13	50	
Number of gestation	Preterm	15	3.0	3.0	1	12	0.187
	Full-term	48	1.0	2.0	1	16	
Maternal parity	Preterm	15	1.0	3.0	0	11	0.454
	Full-term	48	0.0	2.0	0	13	
Age at NS onset (hours)	Preterm	30	72.0	141.7	1	504	*0.000
	Full-term	74	12.0	23.0	1	408	

N, neonatal seizures; ID, interquartile distance; p, value obtained with Mann Whitney U test; *p, significance.

Table 2. Category variables in 30 preterm and 74 full-term infants with neonatal seizures.

Category variables	Gestational age				OR	C.I. OR (95%)	p value
	Preterm		Full-term				
	n	%	n	%			
Male	17	56.6	41	56.1	1.01	0.55-1.86	0.963
Female	13	43.4	32	43.9	0.98	0.38-2.51	0.865
Operative delivery	12	40.0	42	56.7	0.61	0.33-1.14	0.121
Vaginal delivery	18	60.0	32	43.3	0.18	0.76-5.15	0.185
1 minute-SD Apgar	10	33.3	29	39.1	0.74	0.38-1.42	0.357
5 minutes-SD Apgar	3	10.0	9	12.1	0.72	0.12-3.21	0.459
1 minute-D Apgar	13	43.3	48	64.8	0.29	0.10-0.79	*0.006
5 minutes-D Apgar	9	30.0	28	37.8	0.59	0.21-1.63	0.269
NS Recurrence	4	13.3	16	21.6	0.64	0.25-1.64	0.331
Mortality	11	36.6	11	14.8	2.15	1.21-3.83	*0.014

NS, neonatal seizures; OR, odds ratio; CI, confidence interval; SD Apgar, severe depressed Apgar (0 to 3 scores); D Apgar, depressed Apgar (0 to 6 scores); p, value obtained with Fisher's exact test; *p, significance. 1, newborn full-term with ambiguous genitalia.

Table 3. Neonatal seizures types in 30 preterm and 74 full-term infants with neonatal seizures.

NS type	Gestational age				OR	CI OR (95%)	p value
	PN		FT				
	n	%	n	%			
Subtle	8	26.6	54	72.9	0.13	0.05-0.38	*0.000
Tonic	10	33.3	20	27.0	1.35	0.48-3.66	0.520
Clonic	15	50.0	12	16.2	5.17	1.81-14.78	*0.000
Myoclonic	3	10.0	4	5.4	1.94	0.27-12.25	0.320

NS, neonatal seizures; PN, preterm infant; FT, full-term infant; OR, odds ratio; CI, confidence interval; p, value obtained with Fischer's exact test; *p, significance.

Table 4. Probable etiologies in 30 preterm and 74 full-term infants with neonatal seizures.

Etiology	Gestational age				OR	CI OR (95%)	p value
	PN		FT				
	n	%	n	%			
HIE	8	26.6	48	64.8	0.20	0.07-0.55	*0.000
Hypocalcemia	5	16.6	11	14.8	1.15	0.28-4.04	0.817
Hypoglycemia	6	20.0	8	10.8	2.06	0.53-7.55	0.213
PVIH	11	36.6	3	4.0	13.7	3.10-81.39	*0.000
CNS malformation	2	6.6	3	4.0	1.69	0.13-15.51	0.572
Hypomagnesemia	0	0.0	3	4.0	-	-	-
IEM	0	0.0	1	1.3	-	-	-
Meningitis	0	0.0	1	1.3	-	-	-

OR, odds ratio; CI, confidence interval; PN, preterm infant; FT, full-term infant; HIE, hypoxic-ischemic encephalopathy; PVIH, peri-intraventricular hemorrhage; CNS, central nervous system; IEM, inborn errors metabolism; p, value obtained with Fisher's exact test; *p, significance; (-), not observed.

Table 5. Relation between age of onset of neonatal seizures and probable etiologies in 30 preterm and 74 full-term infants.

Etiology	Age of first NS (hours)	Gestational age				OR	CI OR (95%)	p value
		PN		FT				
		n	%	n	%			
HIE	0-72	6	75.0	45	93.7	0.20	0.02-2.97	0.144
	>72	2	25.0	3	6.3			
Hypocalcemia	0-72	3	60.0	8	72.7	0.56	0.04-10.34	0.516
	>72	2	40.0	3	27.3			
Hypoglycemia	0-72	2	33.3	7	87.5	0.07	0.00-1.56	0.062
	>72	4	66.7	1	12.5			
PVIH	0-72	4	36.3	1	33.3	1.14	0.04-84.07	0.725
	>72	7	63.7	2	66.7			
CNS Malformation	0-72	1	50.0	3	100	-	-	-
	>72	1	50.0	0	0.0			
Hypomagnesemia	0-72	0	0.0	0	0.0	-	-	-
	>72	0	0.0	1	100			
IEM	0-72	0	0.0	2	66.6	-	-	-
	>72	0	0.0	1	33.4			
Meningitis	0-72	0	0.0	1	100	-	-	-
	>72	0	0.0	0	0.0			

NS, neonatal seizures; OR, odds ratio; PN, preterm infant; FT, full-term infant; HIE, hypoxic-ischemic encephalopathy; PVIH, peri-intraventricular hemorrhage; CNS, central nervous system; IEM, inborn errors metabolism; CI, confidence interval; p, value obtained with Fisher's exact test; (-), not observed.

FT (p=0.000) and more peri-intraventricular hemorrhage (PVIH) (p=0.000). In 65 neonates (62.5%), of whom 12 (40.0%) were premature and 53 (71.6%) were full-term, we noted a single probable etiology for NS. In 19 (18.2%) neonates, of whom 10 (33.3%) were PN and 9 (12.1%) FT, it was not possible to determine the etiology. In 15 (14.4%) of the neonates

we observed epileptic status, 12 (16.2%) in FT and 3 (10.0%) in PN.

Table 5 shows the relation between the age at the onset of the seizures and etiology. In HIE, the onset of NS is early in both FT and PN, while in PVIH, which predominates in PN, seizure onset was slightly delayed.

DISCUSSION

It is well recognized that seizures are more common in the neonatal period than in any other stage of life³. In the NS literature we find excellent studies, such as those by Mizrahi and Kellaway¹⁶, with detailed discussions on various aspects, but not taking into account the consequences of gestational age. Currently, with medical and technological advances in ICU, 85% of PN survive¹⁷, thus turning into a category with its own characteristics in relation to its immature central nervous system and their neuronal lesion mechanisms^{18,19}. In this way, in relation to NS, it is important to bear in mind the differences between PN and FT group.

Our study had three parameters which were fundamental in attaining its objectives: 1) to be prospective in view of the neonatal period; 2) to use a population that had been treated exclusively in ICU dividing it into two groups, according to gestational age and rigorous clinical observation; and 3) using stimulation and restraint techniques to accurately define NS. Studies based on clinical data are uncommon in the literature, however we would like to mention the study of Brunquell et al.²⁰ and the similarity of their approach to our emphasis on clinical observation. Saliba et al.²¹ also emphasize gestational age as a NS risk factor and discuss the difference between term and preterm neonates.

The incidence of NS in our study was 6.9% this was slightly lower than that found by Sheth who reported an incidence of 8.6% in 4165 newborn admitted to ICU²². This finding can be partly explained by the reduced number of public ICU in Natal and by the low socio-economic level of the study population, that have not access to private ICU. Our figures exceed those of Brunquell et al.²⁰. This difference may be related to the method of these authors, who performed a retrospective study, using data from medical records. In the electroclinical study by Sheth²³, the seizures correlated with EEG alterations in 63% of PN at 28 weeks and in 77% of FT. The lower neuronal organization may explain the lower clinical and electroclinical expressiveness of the condition in PN with a resultant lower seizure frequency with our study.

An important finding in this study was the statistically significant difference for the time of NS onset, which occurred later in the premature. Unlike of Sheth et al.²² that reported seizures manifested earlier in infants <30 weeks and >36 weeks gestational compared with neonates 30 to 36 weeks. This difference might have etiological reasons of the seizures:

HIE was the predominant etiology in the FT, causing early-onset NS in the first 48 hours of life²⁴. This finding is in agreement with the data reported by Ahn et al.²⁵ who correlated time of NS onset and underlying neurological lesions. On the other hand, in PN peri-intraventricular hemorrhage was the most frequent etiology and its clinical picture intensifies after 72 hours of life, thus causing later seizures manifestation^{3,5,26}. However, when HIE was the likely etiology, NS had early-onset in both groups. This finding agree with reports stressing neonatal asphyxia as the most frequent cause of early-onset NS^{3,16}. Whereas Calciolari et al.²⁴ reported neonatal asphyxia as the predominant etiology in both PN and FT. The NS are caused by hypoxic-ischemic encephalopathy in 50 to 60% of neonates, independent of gestational age, according to Volpe³. However, determining the exact etiology of the seizures is very difficult, since a large number of etiological factors may coexist particularly: HIE, metabolic disorders and intracranial hemorrhages. In this study, 62.5% of the neonates were presumed to have an etiology, while the number of babies with undetermined etiology (18.2%) was substantial. This impossibility of pinning down likely etiologies was also due to the unavailability of certain diagnostic tests. For instance, access to cranial ultrasounds examination was possible in only 55.7% of the neonates selected. Despite these difficulties, our overall findings were not basically different from current literature.

The presence of severe depressed Apgar (0 to 3 scores) did not show significant statistical difference between the groups. As to depressed Apgar (0 to 6 scores), there was a significant statistical difference at 1 minute of life, with lower frequency in the PN. This difference dissipated at 5 minutes probable due to reanimation techniques promptly initiated at birth in the delivery room. PN have greater risk for perinatal asphyxia and need for reanimation in the delivery room due to deficiency of the pulmonary surfactant system, they are most susceptible to heat loss, have the greatest risk for intra-uterine infection and the most fragile cerebral capillaries²⁷. Surprisingly, our data of PN showed lower frequency of depressed Apgar when compared with FT. These figures however, could be deceptive due to our emphasis being placed on NS. According to Volpe³, the parameter of asphyxia based on Apgar scores has greater predictive value for the neurological outcome rather than for NS.

Subtle seizures were the most frequently observed clinical type of NS in our study, present in 59.6% of

the newborn, similar to the data reported by Calciolari et al.²⁴ and by Brunquell et al.²⁰. Arpino et al. referred to generalized tonic seizures as the most frequent seizure type and in 71% of the neonates, an association of more than one clinical type of NS was observed²⁸. Ronan et al. reported that tonic seizures predominated in FT, and clonic seizures were equally common in both groups²⁹. When we compared the two groups, subtle seizures were most frequently observed in FT, in accordance with the literature^{3,16,24}. In PN, however, clonic seizures were the most frequent. This results were too observed by Scher et al.³⁰ who used electro clinical data.

The general mortality rate of the sample was similar to that observed in the 1990s, which was around 20%²⁶ and, in our material higher in PN ($p=0.014$). The odds ratio indicates that the risk of death in PN is twice as high as that of FT. The historically greater mortality rate of PN is due to the wealth of serious pathologies of to prematurity and therefore unrelated to presence or absence of NS. In conclusion, we wish to point out that: 1) PN develop NS later, probably related to the etiologies of the seizures; 2) etiologically, there is a predominance of PVIH in PN and of HIE in FT; 3) clonic seizures are most frequent in PN and subtle seizures in FT; and 4) the mortality rate is determined by underlying severe pathology associated with prematurity and not by the NS as such.

We also wish to place great emphasis on the use of stimulating and restraining maneuvers for provocation or termination of seizures - especially in view of the unavailability of video-EEG-monitoring. Such maneuvers will enrich the clinical approach to NS - not only in the ICU but also in daily clinical practice.

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