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SEIZURE RECURRENCE IN INFANTS WITH NEONATAL CONVULSIONS

A FOLLOW-UP STUDY

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SUMMARY — Twenty three infants with neonatal seizures were followed prospectively to a mean age of 11 months. Only 2 were pre-term and birth weight ranged from 1700 to 4230 grams, with 17 male and 6 female infants. Hypoxic-ischemic encephalopathy was the most common etiology (82.6%). Focal clonic convulsions were the predominant seizure type, present in 7/16 infants in which the seizure type could be identified. All infants had a neurological examination and EEG, and 18 had a cranial ultrasonography performed at the follow-up. Anticonvulsant medication was discontinued, if follow-up EEG and neurological examination were normal. At the follow-up, seizure recurrence was observed in 7/23 (30%) infants. Abnormal EEG, neurological examination and cranial ultrasonography were statistically correlated with seizure recurrence. We conclude that infants with neonatal seizures can remain free of anticonvulsant medication provided they have normal neurological examination, EEG and cranial ultrasonography.

KEY WORDS: newborn, neonatal convulsion, seizure recurrence.

Recorrência de crises convulsivas em crianças com convulsões neonatais: estudo evolutivo.

RESUMO — Vinte e três crianças com crises convulsivas neonatais foram seguidas, prospectivamente, até idade em média de 11 meses. O peso ao nascimento variou de 1700 a 4230 gramas; 2 eram pré-termo; 17 eram meninos e 6, meninas. A encefalopatia hipóxico-isquêmica foi a etiologia mais frequente (82,6%). Houve predomínio das crises clônicas focais, presentes em 7/16 crianças nas quais o tipo de crise foi identificado. Todas as crianças foram submetidas a exame neurológico e avaliação eletrencefalográfica e, em 18 delas, foi realizado exame ultrassonográfico (US) de crânio durante o seguimento ambulatorial. A medicação anticonvulsivante foi interrompida se o EEG e o exame neurológico eram normais no seguimento. A recorrência de crises foi observada em 7/23 crianças (30%). Houve relação estatisticamente significante entre a recorrência de crises e anormalidades do exame neurológico, EEG e US de crânio. Concluímos que as crianças com crises convulsivas neonatais podem permanecer sem medicação anticonvulsivante desde que não apresentem anormalidades ao exame neurológico, ao EEG e ao US de crânio.

PALAVRAS CHAVE: recém-nascido, convulsão neonatal, recorrência de convulsão.

Seizures are a common neurologic condition that reflect many central nervous system (CNS) disorders and represent the most distinctive signal of neurological disease in the newborn period. The precise frequency of neonatal seizures cannot be accurately estimated because many of the subtle manifestations of the convulsions undoubtedly have been either underestimated or overestimated. Previous studies have reported a range in the incidence of clinical neonatal seizures from 0.5% of term births [8] to 20.2% of pre-term infants [15]. Most of the studies of neonatal seizures

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show a predominance of male infants [2,10,13]. The identification of seizures presents a significant clinical problem in caring for newborns. They are difficult to recognize and consequently the determination of etiology and initiation of appropriate therapy may be delayed. Subtle and multifocal clonic were the most common seizure types in a retrospective review of 150 newborns evaluated at the same medical center [3]. Clonic seizures have a good correlation with electrographic seizures activity while the subtle type has an inconsistent or no correlation at all [11]. EEG studies in newborns with neonatal seizures showed that the majority of electrographic seizures occur without any clinical seizure activity [8,11,12]. As much as 79% of the seizures can be «occult»: electrographic seizure activity without clinical manifestations [4]. Hypoxic-ischemic encephalopathy is by far the most common etiology in both pre-term and term infants [14,16]. The majority of seizures are observed in the first 48 hours of life [3,5]. The prognosis for infants with seizures in the neonatal period has improved over the years. Volpe [16] reported a decrease in mortality rate before and after 1969, from 40 to 15%, while the incidence of neurological sequelae (mental retardation, motor deficits and seizures) in survivors increased from 20 to 30%. Etiological factors are absolutely important when interpreting results. Thus, hypoxic-ischemic encephalopathy, CNS malformations, severe intracranial hemorrhage have a high rate of neurological sequelae while hypocalcemia, subarachnoid heemorrhage and hypoglycemia are seldom associated with bad outcome. Other factores related to prognosis are the neurological condition of the newborn [13,17] and the EEG, in the neonatal period [2,17] and at follow-up [2,13]. Abnormalities on the neonatal CT scan were related to neurological sequelae in the long-term follow-up [2]. The incidence of epilepsy in infants with neonatal seizures is not high, ranging from 15 to 25% [1,13,17], depending on the etiology of the neonatal convulsions.

This is a prospective study of infants with neonatal seizures. The anticonvulsant medication was discontinued, as early as possible, based on clinical and electrographic criteria. We were interested in studying some risk-factors that could be related to recurrence of seizures at follow-up.

MATERIAL AND METHODS

Twenty three infants wits neonatal seizures that attended the Child Neurology Outpatient Clinic of the Clinics Hospital of the University of São Paulo, from January 1987 to February 1989, were enroled in the study. Fifften infants were inborn and 8 were referred from other institutions. Only 2 were pre-term and birth weight ranged from 1700 to 4230 g, with 17 male and 6 female infants. The general data of the study group are shown in Table 1. The seizures occurred between days 1-23. In 17 cases seizures were observed in the first two days, in 3 during the first week, and in 3 after the first week during the first month. Hypoxic-ischemic encephalopathy (HIE) was the most frequent etiology, present in 19 cases (82.6%), followed by metabolic in 3 (13%), and dysgenetic disorders in 2 (8.6%), one with corpus callosum agenesis and one with Down syndrome. No etiological factor could be detected in two infants and more than one etiology was involved in 3.

We were able to identify the seizure type in 16 infants. Clonic seizures were observed in 15 infants. Four were generalized, 4 multifocal and 7 focal. One case had generalized tonic seizures and another developed status epilepticus during the newborn period. Phenobarbital was the only drug used in 15 cases. Phenitoin was associated in 3 cases and carbamazepine in 2. Three infants were free of drugs when first seen at the outpatient clinic.

The follow-up visits were scheduled at 1, 3, 6, 9 and 12 months and each 6 months from there on. The mean follow-up period of the study group was 11 months. At each visit the infants had a full neurologic examination, but only the last one was considered for analysis. All infants had at least one EEG performed during the follow-up. Only 7 infants had electrographic evaluations performed during the neonatal period. Eighteen infants had cranial ultrasonography (US) examination and 7 had a CT scan examination during the follow-up period.

Neurological examination, electroencephalographic and ultrasonographic abnormalities were considered as risk factors and correlated with seizure recurrence at follow-up. Fischer test was used for statistical analysis and significance level at $p=0.05$.

Table 1 — General data of the study group.

Case	Etiology	Seizure type	Onset (day)	Follow-up (months)	EEG	US	Neu.Ex.	Seizure Recurrence
1	unknow	focal clonic	23	18	nl	nl	nl	no
2	H.I.E.	focal clonic	20	7	nl	nl	nl	no
3	H.I.E.	focal clonic	4	2	nl	nl	nl	no
4	H.I.E.	focal clonic	1	18	nl	nl	nl	no
5	unknow	focal clonic	1	10	anl	—	anl	yes
6	H.I.E.	unknown	1	5	nl	anl	anl	no
7	CCA+HypoCA	general.clonic	2	13	nl	anl	anl	yes
8	H.I.E.	status epilept.	1	6	anl	anl	anl	yes
9	H.I.E.	unknown	2	13	anl	—	anl	yes
10	H.I.E.	unknown	2	12	nl	nl	nl	no
11	H.I.E.	general.clonic	1	9	nl	anl	anl	no
12	H.I.E.	unknown	1	3	anl	anl	anl	yes
13	H.I.E.	general.tonic	1	9	nl	—	anl	no
14	H.I.E.	general.clonic	2	7	nl	nl	nl	no
15	H.I.E.	unknown	1	12	nl	—	nl	no
16	H.I.E.	multifocal clonic	1	13	nl	—	nl	no
17	H.I.E.+HypoMg	focal clonic	3	6	nl	nl	nl	no
18	H.I.E.+Down	general.clonic	2	8	nl	nl	anl	yes
19	Hypoglycemia	unknow	20	12	nl	nl	nl	no
20	H.I.E.	multifocal clonic	4	12	nl	anl	anl	no
21	H.I.E.	multifocal clonic	1	23	anl	anl	anl	yes
22	H.I.E.	multifocal clonic	1	24	nl	nl	nl	no
23	H.I.E.	focal clonic	1	11	nl	nl	anl	no

H.I.E., hypoxic-ischemic encephalopathy; CCA, corpus callosum agenesis; HypoCa, hypocalcemia; HypoMg, hypomagnesemia; nl, normal; anl, abnormal.

RESULTS

The anticonvulsant drugs were discontinued if the infant was seizure free and had normal follow-up EEG examination. The time for discontinuing medication varied from 15 days to 4 months of age. If seizure recurrence was observed, anticonvulsant medication was started again. Seven infants were still on medication when last seen.

Seizure recurrence was observed in 7 infants (30%), between 2-6 months (mean 4m.). Data concerning seizure recurrence and the risk factors studied are shown in Table 2.

Neurological abnormalities were detected in 12 infants (52.1%). Eight infants were diagnosed as having cerebral palsy; the other 4 had mild developmental delays without focal neurological signs. Eleven infants had normal neurological examination at the last follow-up visit. There was a significant correlation between neurological abnormalities at follow-up and seizure recurrence ($p=0.0006$). None of the infants with normal neurologic examination had seizures during the follow-up period, while 7/12 neurologically abnormal infants had seizure recurrence.

Table 2 — Seizure recurrence and follow-up EEG, neurological examination and cranial US.

		Seizure Recurrence			
		Yes	No	Total	
EEG	NL	2	16	18	p=0.0006(*)
	ANL	5	0	5	
	Total	7	16	23	
Neur.Ex.	NL	0	11	11	p=0.029(*)
	ANL	7	5	12	
	Total	7	16	23	
US(+)	NL	1	10	11	p=0.044(*)
	ANL	4	3	7	
	Total	5	13	18	

NL, normal; ANL, abnormal; (+), *5 cases had no cranial US, 2 with and 3 without recurrence;* (*), *significant.*

Seven infants had EEG examination during the neonatal period. Two were abnormal, one with periodic and focal activity, and the other with multifocal epileptic activity. Both had abnormal EEGs at follow-up and developed seizures. Five infants (21.7%) had abnormal follow-up EEGs, 4 with epileptic activity and one with asymetric activity. Follow-up abnormal EEGs and seizure recurrence were significantly related (p=-0.029). All 5 infants with abnormal EEGs had seizures during follow-up compared with only 2/18 infants with normal tracings.

Cranial US showed abnormalities in 7/18 infants. The abnormalities consisted of varying degrees of ventricular dilatation associated or not with indirect signs of cortical atrophy. At follow-up, among 7 infants with abnormal US 4 experienced seizure recurrence, compared with only 1/11 with normal examination. Abnormal cranial US was statistically associated with seizure recurrence (p=0.044). Of the five cases that had no cranial US, 2 had seizure recurrence, and 3 were free of seizures at follow-up.

The CT scans were abnormal in all 7 cases, showing the same imaging picture detected on the US.

COMMENTS

The possibility of predicting recurrence of seizures with a reasonable accuracy, in infants who experienced them in the newborn period, is a fact that has implications in the management of neonatal convulsions. The maintenance of anticonvulsant drugs and for how long should they be administered are decisions often taken on empirical basis and the subject is controversial.

Gal & Boer [10] reported no seizure recurrence after 6-18 months of follow-up in 10 infants with neonatal convulsions that had the anticonvulsant therapy discontinued shortly after seizure control. Only one infant had an abnormal EEG and the length of anticonvulsant therapy ranged from 5 to 94 days. They suggest that drug therapy could be stopped in the neonatal unit, in seizure controlled infants. Bergman et al.[1] recommended discontinuing drugs after two seizure-free weeks based on the low incidence (8%) of frequent seizures in a population of infants with neonatal convulsions.

Volpe [16] considers EEG, seizure etiology and the neurological examination as the main factors implicated in the decision of interrupting medication in neonatal

seizures. If the neurological examination is normal the drugs are discontinued either in the neonatal period or at the follow-up. If abnormal or doubtful, drug therapy is maintained, and at 3 months the the evaluation is repeated. If normal, the drug is discontinued. If the infant has an abnormal or doubtful neurological examination, an EEG is performed. Only infants with paroxysmal tracings will be kept on medication.

Ellison [6] developed a system using a weighted scoring technique that combines EEG, seizure etiology, neurologic examination, type and length of seizures, and birth weight to predict subsequent epilepsy. Each item is scored 0-2. In the neonatal period, infants with 4 points or less have one drug discontinued (if only one drug is being used they remain medication free). The evaluation is repeated each 3 months, seizure length and type item being replaced by seizure recurrence. Infants who score 5 points or less have their medication discontinued.

Our data showed that abnormal neurological examination, EEG and cranial US abnormalities were significantly related to seizure recurrence in infants with neonatal convulsions. All infants with abnormal EEGs experienced seizures at follow-up. None of the infants with a normal neurological examination had seizure recurrence. Only 1/10 infant with normal cranial US experienced recurrence. Sixteen (70%) infants had no recurrent seizure at follow-up.

Brod et al.[2] found a significant and independent correlation among initial EEG, subsequent EEG, CT scan and continued administration of antiepileptic drugs, in a retrospective study of 48 infants with neonatal seizures. Follow-up neurologic examination was significantly related to successful drug discontinuation only in the term infants group. The crieteria for discontinuing medication were a non-focal neurologic examination and normal subsequent EEG. There were no significant correlations between sex, Apgar scores, weight, etiology of seizure and initial neurologic examination, and the successful tapering of medication. Thirty-four infants were tapered from antiepileptic drugs. Thirty-one infants had no recurrent seizure.

Scarpa et al.[13] followed 51 infants with neonatal seizures from 1-8 years. Drugs were discontinued after 4 to 19 months, based on clinical, etiological and electrographic criteria. Thirty-nine cases had no relapse since medication was discontinued, while 4 had seizure recurrence. In 8 cases seizures were never controlled. They found a significant correlation between length of treatment and durantion of EEG abnormalities. EEG abnormalities were also significantly related with clinical outcome and seizure recurrence.

Watanabe at al.[17] found a recurrence rate of 25%, in a group of 264 infants with neonatal seizures followed up for more than 3 years. There were no significant differences as to the type and duration of seizures between those who developed epilepsy and those who did not. In the perinatal asphyxia group with an overall recurrence rate of 30% they observed that those with normal neurological findings did not develop epilepsy, whereas 51% of those with severely abnormal neurological examination developed epilepsy. The more abnormal the neonatal background EEG, more often they observed recurrent seizures.

Our study suggests that infants with neonatal seizures can remain free of medication provided the neurological, electroencephalographic and cranial US examinations are normal in the follow-up. The study group was mainly composed of infants with perinatal asphyxia, which is certainly the main etiology found in neonatal units. We could not adequately study the neonatal variables as EEG, neuroimaging studies and neurological examination. Thus, our conclusions would be particularly helpful for the clinician who has to take decisions, concerning long-term treatment of neonatal seizures, without a thorough knowledge of perinatal events.

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