Arq Neuropsiquiatr 2005;63(1):14-19

PROGNOSTIC VALUE OF NON-REACTIVE BURST SUPPRESSION EEG PATTERN ASSOCIATED TO EARLY NEONATAL SEIZURES

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ABSTRACT - Seizures are the most frequent neurological event in newborns and clinical data suggest that etiology is the dominant factor in long term outcome. However, there are consistent background EEG abnormalities associated to neonatal seizures that are usually related to unfavorable outcome as the burst - suppression pattern. *Objective:* The objective of this study was to correlate clinical and EEG features associated to long - term outcome of newborns with non - reactive burst - suppression (BS) EEG. *Method:* Newborns included in the study were selected from our database and had conceptional age (at the time of first EEG) >37 weeks, EEG recordings with non - reactive BS available for review and clinical follow up. *Results:* 12 newborns met inclusion criteria, 50% had seizures in the first day of life. Seizures became refractory to treatment in all of them. In 50% the etiology of seizures was considered cryptogenic, 33% had inborn errors of metabolism and 17% had clinical history and neuroimage suggestive of hypoxic-ischemic encephalopathy. The follow-up showed that 7/12 infants deceased, 3 during the first year of life, and one in the neonatal period. All the survivors had severe developmental delay and multifocal neurological impairment. 92% developed refractory epilepsy, 58% were latter diagnosed with West syndrome. *Conclusion:* The non-reactive BS pattern may appear related to many neonatal neurological disorders and is associated with early and refractory neonatal seizures. It is clearly associated with elevated morbidity and mortality and to the development of post-neonatal epilepsy.

KEY WORDS: neonatal EEG, neonatal seizures, burst-suppression pattern, neonatal epileptic syndromes.

Valor prognóstico do EEG com padrão de surto-supressão não reativo associado a convulsões neonatais precoces

RESUMO - Convulsões representam o evento neurológico mais freqüente no período neonatal e a etiologia das crises parece ser o aspecto clínico mais associado ao prognóstico a longo prazo. Entretanto, existem padrões anormais de EEG, que de forma consistente relacionam-se a prognóstico, entre eles o padrão de surto - supressão. Objetivo: Este estudo teve como objetivo correlacionar aspectos clínicos e eletroencefalográficos associados a prognóstico em longo prazo de recém - nascidos (RN) com padrão de surto - supressão não reativo no EEG. *Método:* Foram selecionados para este estudo RN com EEG neonatal realizado no Laboratório de Neurofisiologia Clínica do Hospital São Lucas da PUCRS e acompanhados na mesma instituição, com idade concepcional superior a 37 semanas (na data do EEG), cujos registros estivessem disponíveis para revisão. *Resultados:* Foram incluídos 12 RN, 50% apresentaram crises convulsivas a partir do primeiro dia de vida. Em todos as convulsões eram refratárias ao tratamento medicamentoso. Em 50% a etiologia foi considerada criptogênica, 33% apresentavam erros inatos do metabolismo e 17% tinham história clínica e achados de neuroimagem sugestivos de encefalopatia hipóxico - isquêmica. O seguimento clínico demonstrou que 7/12 evoluíram para óbito, sendo 3 durante o primeiro ano de vida e um no período neonatal. Os sobreviventes apresentavam grave comprometimento do desenvolvimento neuropsicomotor e déficits neurológicos múltiplos, 92% seguiram com epilepsia refratária e 58% evoluíram para síndrome de West. *Conclusão:* O reconhecimento de padrão de surto - supressão não reativo no EEG neonatal pode ser relacionado a diversas doenças neurológicas e é associado a convulsões precoces e refratárias. Existe também definida associação entre este padrão e elevada morbi-mortalidade neonatal além do desenvolvimento de epilepsia pós-neonatal.

PALAVRAS-CHAVE: EEG neonatal, convulsões neonatais, síndromes epilépticas neonatais, surto - supressão.

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Received 24 May 2004, received in final form 14 August 2004. Accepted 2 October 2004.

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Seizures are the most frequent neurological event in newborns[1]. Furthermore, the incidence of seizures in the neonatal period is greater than at any other period of life, ranging from 1.8 to 5.1/1000 live births[2-4]. The outcome of newborns with seizures has been evaluated by many authors in previous studies[5-8]. There is no clear consensus on how seizures *per se* are responsible for long term neurological or cognitive sequelae. However, clinical data suggest that etiology is the dominant factor in long term outcome. The incidence of epilepsy following neonatal seizures has been estimated in previous studies and it varies from 17% to 30%[9-14]. Since the early manuscript from Monod[15] many other studies concerning the power of neonatal EEG to predict neurological outcome have been developed. There are consistent background EEG abnormalities that are usually associated to unfavorable outcome as low voltage and burst - suppression pattern (BS)[15-21] .

BS, an abnormal EEG pattern, included among the broad spectrum of discontinuity in neonatal EEG, is termed reactive when it can be interrupted by stimulation[22, 23] and non reactive in the contrary, this last pattern has been traditionally associated with unfavorable outcome[15,21,24,25]. BS pattern is also the hallmark of two specific epileptic neonatal syndromes, early myoclonic encephalopathy and early infantile epileptic encephalopathy[26,27]. And it can also happen associated to severe central nervous system disorders such as perinatal asphyxia, inborn errors of metabolism, acquired or congenital infection, dysgenesis.

The aim of this study was to evaluate clinical and EEG features associated to long - term outcome of newborns with early - seizures and non- reactive burst - suppression EEG.

METHOD

Patients – This retrospective transversal study included infants admitted in the Neonatal Intensive Care Unit of the Hospital São Lucas (University Hospital from PUCRS School of Medicine, Porto Alegre -RS) between January 1984 and June 2002. From our EEG database we selected all infants with early seizures and burst-suppression pattern in the first neonatal EEG. To be included in the study, newborns should have conceptional age (at the time of first EEG) >37 weeks, EEG recordings available for review and follow up in our Pediatric Neurology outpatient clinic.

Perinatal data were extracted from medical records and included gestational age, concepcional age at the firs burst- suppression EEG, Apgar score in the 1st and 5th minute of life, birth weight, sex, age of first seizure, type and frequency of seizures, neurological examination, laboratory screening for metabolic and infectious disorders and report of neuroimage studies.

For outcome analyzis we considered the development of post-neonatal epilepsy, neurodevelopment delay and decease. Neuropsychomotor development was based on report of clinical neurological examination and results of Denver II screening test[28].

EEG recordings – The EEGs were performed on a 16 channel EEG and consisted of 11 channels of EEG, electro-oculogram, submental electromyogram, nasal and abdominal respiratory monitoring and electrocardiogram. Paper speed was 15 mm/s, and for the EEG we used the time constant of 0.3 s; sensitivity 10 µv/mm and 70 Hz high linear frequency filter. The electrodes were placed based on the 10-20 system as modified for newborns[29]. The states of the newborn and all the movements during the exam were recorded on the paper by the technician. Each exam lasted at least 50 minutes (or until a complete sleep cycle was recorded). In the cases where a video - EEG was available seizures observed by the technicians were reviewed. A neurophysiologist expert in neonatal EEG unaware of the outcome retrospectively reviewed EEGs.

For analysis we considered the definition of burst - suppression pattern as: periods of inactive background that may last from 2 to 10 seconds usually, interrupted by high voltage bursts lasting 1 - 10 seconds, composed of mixed features: irregular delta and theta waves with variable amounts of interspersed spikes and sharps waves[21] (Fig 1).

In each EEG (one per newborn), we evaluated different parameters including mean burst duration, maximal amplitude of the burst, amount of spikes in the burst, mean duration of the interburst interval, maximal duration of the interburst interval, presence of electroencephalographic seizures and presence of sharp waves in the interburst[19].

The predominant interburst interval duration was defined as the mean interburst interval duration within a given EEG. Mean burst duration, mean interburst interval duration and maximal burst duration were mesured in seconds, maximal amplitude of the burst was measured in microvolt, the amount of spikes among the burst was visually counted[19].

For statistical analysis the outcome was related to clinical and EEG features by means of bivariate analysis (Student's T test, Fischer's exact test and χ^2).

This study is part of the project" Risk factors for developing epilepsy after neonatal seizures", approved by the ethical and scientific committees of our institution. Ethical issues concerning retrospective studies were followed in this protocol.

RESULTS

During the study period 706 high-risk newborns were submitted to neonatal EEGs. Among

them 30 (4.2%) presented at least one EEG with burst-suppression pattern and 12 met the inclusion criteria of our study. The group consisted of 7 female and 5 male babies, with Apgar scores varying from 4 to 9 at the 1st minute and 4 to 10 at the 5th minute of life. The birth weight varied from 1750 to 3665 grams. Clinical characteristics and follow up of the newborns are described on Table 1.

All newborns started with seizures during the first week of life and half of them had seizures in the first day of life. Most of the newborns presented more than one type of seizures, in all newborns seizures become refractory to treatment with antiepileptic drugs. The most prevalent type of seizure was focal tonic.

Evaluating neurological status all patients had an obvious encephalopathy from birth with marked hypotonia and hypoactivity. Mechanical ventilation was required in 4 (33%).

Neuroimage studies were available for review in 10 children. 6/10 computed tomography (TC) were considered within normal limits, two had white matter hipodensity, one enlarged ventricles and one periventricular calcifications. Besides the CT scan, 2 newborns were submitted to brain magnetic resonance image (MRI), which confirmed previous findings.

After an extensive evaluation for possible etiology of seizures in 6 newborns it was considered cryptogenic, 4 had inborn errors of metabolism and 2 had clinical history and neuroimage suggestive of hypoxic - ischemic encephalopathy.

The follow-up showed that 7/12 infants deceased, three during the first year of life, and one in the neonatal period. Duration of follow up in the survivors varied from 12 to 24 months as expressed on Table 1. All the survivors had severe developmental delay and multifocal neurological impairment in the moment of the last evaluation. Eleven newborns (92%) developed refractory epilepsy, and 7 of them (58%) were latter diagnosed with West Syndrome.

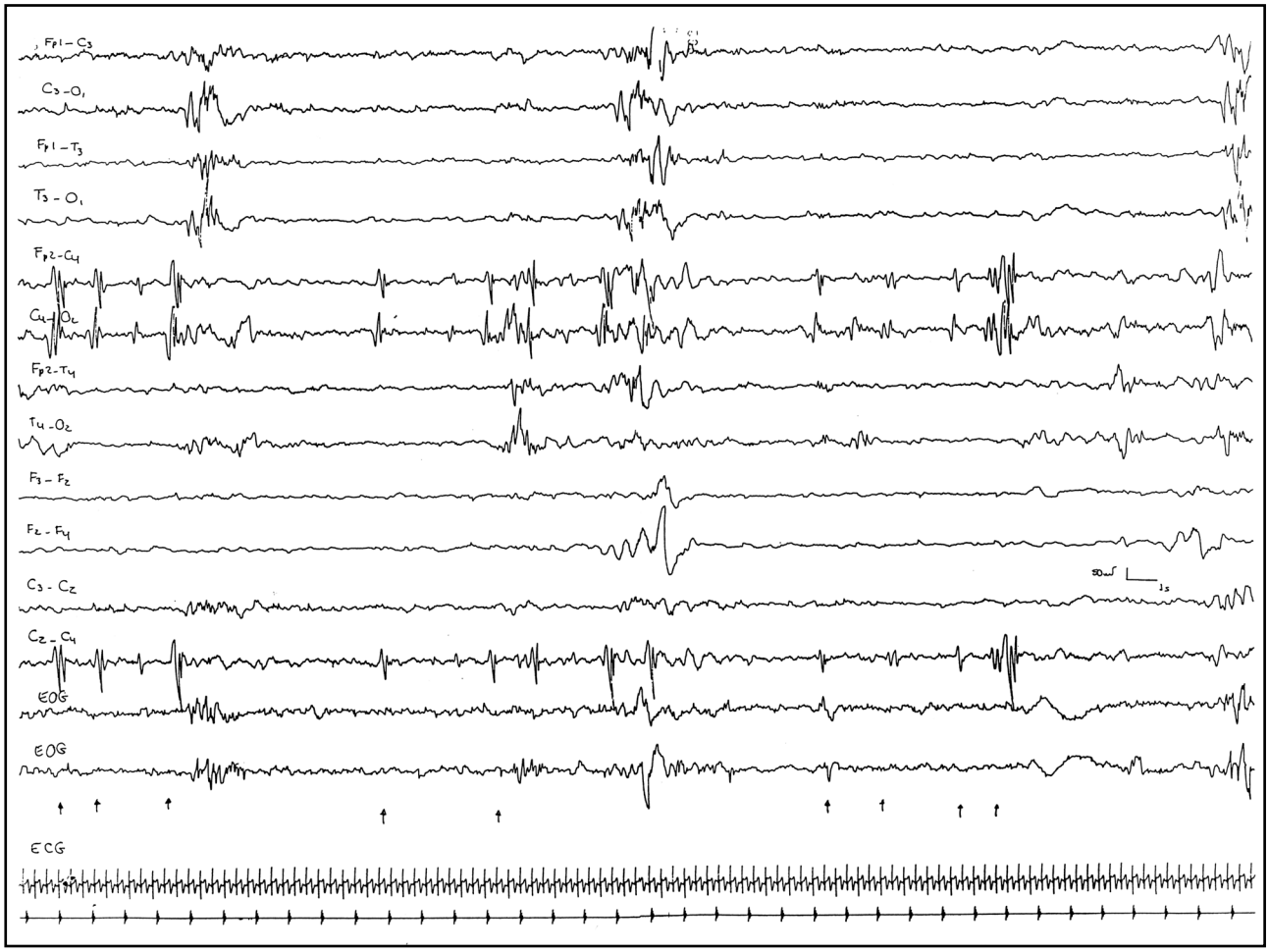

Fig 1. Neonatal EEG showing burst suppression pattern in a newborn with multiple seizures type, refractory to antiepileptic drugs. Arrows indicate myoclonic seizures. 15mm/s.

Table 1. Clinical characteristics at the neonatal period and outcome.

	Sex	BW	Apgar 5′	GA	FS	TS	NE	Neuroimage	Etiology	Death	Epilepsy	Development
1	F	NA	9	40	2	FT/M	Hypotonia	NA	Piridixine dependent	—	West syndrome	Delayed (2 year)
2	F	3000	8	40	1	FT/FC	Hypotonia/ Hypoactivity	Ventriculomegalia (CT Scan)	Cryptogenic	—	Refractory epilepsy	Delayed (2 year)
3	M	3200	10	39	1	FT	Hypotonia/ Hypoactivity	NA	Metabolic disease	6m	West syndrome	Delayed
4	F	3000	9	40	1	FT/FC/M	Hypotonia/ Coma/MV	Normal (CT Scan)	Metabolic disease	36 m	West syndrome	Delayed
5	M	3800	6	40	4	FT	Hypertonia	Normal (CT Scan)	Hipoxic ischemic enceplalopathy	72 m	West syndrome	Delayed
6	F	3300	4	39	1	FT/FC	Hypertonia/ Hypoactivy/MV	Frontal white matter hipo desity (CT Scan)	Hipoxic ischemic enceplalopathy	18 m	Refractory epilepsy	Delayed
7	M	3600	4	41	3	FT/M	Hypotonia/ Hypoactivity/ Coma/MV	Normal (CT Scan)	Cryptogenic	3m	Early myoclonic enceplalopathy	Delayed
8	F	2700	9	39	2	FT	Hypoactivity/MV	Normal (CT Scan)	Cryptogenic	—	West syndrome	Delayed (1 year)
9	M	3600	9	36	2	FT/S	Active	Normal (CT Scan)	Cryptogenic	—	West syndrome	Delayed (1 1/2 year)
10	F	2500	8	36	1	FT/S	Hypotonia/ Hypoactivity	Difuse white matter hypoden sity (CT Scan)	Piridixine Dependent	26d	Refractory epilepsy	
11	F	1700	7	35	1	FT/M/S	Hypotonia/ Hypoactivity	Periventricular calcifications (CT Scan) Hyperintensity in white matter (MRI)		3m	Early myoclonic encephalop	Delayed
12	M	3200	9	40	1	FT	Hypotonia	Normal (CT SCAN / MRI)	Cryptogenic	—	West syndrome	Delayed (1 year)

Sex: F, female; M, male; BW: birth weigh in grams; GA, gestacional age in weeks; FS, age in days of first seizure; TS, type of seizure (FT, focal tonic; FC, focal clonic; M, mioclonic; S, spasms); NE, neurologic status in the neonatal period (MV, mechanical ventilation); Death, age of death (m, month; d, days); NA, not available; Encephlop, encephalopathy.

Table 2. Neonatal EEG and follow up EEG.

	GA	CA	MIBI	MAXIBI	Sharp IB	Burst amp	Burst Spike	M Brust	EEG Sz	Follow-up EEG	Age Follow EEG
1	40	41w 6d	7.5	20	No	>150	>3	3	Yes	Hypsa-rrhythmia	1y 10m
2	40	42w	2.0	3	Yes	<150	<3	2	No	Multifocal	1y 8m
3	39	40w 5d	6.0	15	No	>150	>3	2	No	Hypsa-rrhytmia	6m
4	40	40w 1d	5.5	10	No	<150	>3	5.5	No	Hypsa-rrhytmia	3y
5	40	42w	4.0	7	No		>3	4	Yes	Hypsa-rrhytmia	18m
6	39	41w	4.0	8	No	>150	>3	2	No	Burst-Suppression	1m
7	41	42w	2.0	7	Yes	>150	>3	7	No	Burst-Suppression	3m
8	39	42w	2.0	7	No	<150	>3	4.5	No	Multifocal	10m
9	36	38w	3.0	8	No	<150	>3	2	No	Hypsa-rrhytmia	1y 4m
10	36	38w	2.5	7	No	>150	>3	4	No	Multifocal	20d
11	35	42w	21	75	Yes	>150	>3	2	Yes	Burst-Suppression	2m
12	40	40w	3.0	8	Yes	>150	>3	3.5	Yes	Hypsa-rrhytmia	6m

GA, gestational age in weeks; CA, conceptional age in weeks and days; MIBI, mean interburst duration; MAXIIBI, maximum interburst duration; SharpIB, presence of sharp waves among IBI; Burst amp, amplitude of burst microvolts; Burst Spike, number of spikes in each burst; M Burst, mean burst duration; EEG Sz, electrographic seizure).

EEG features analyzed showed mean interburst duration ranging from 3-21 seconds (5.2±5.2), maximal interburst duration from 3 to 20 seconds (8.9±4.4), mean burst duration from 2 to 7 seconds (3.4±1.6). Burst amplitude was higher than 150μV on 7/12 EEGs. Electrographic seizures were observed on 4 EEGs (33%), sharp waves during the interburst interval were recorded in 4 EEGs (33%), in 11 EEGs the burst had more than 3 spikes (92%).

All newborns in our sample had abnormal follow up EEGs (3/12 had persistent burst-suppression, 6/12 developed hypsarhythmia, 3/12 multifocal spikes) (Tabela 2).

The results of the bivariate analysis comparing clinical outcome to EEG features did not showed significant association between the parameters studied.

DISCUSSION

In this paper we have reviewed clinical and EEG characteristics of newborns with early refractory seizures and non - reactive BS pattern. As expected we have find that this pattern is associated to unfavorable outcome. Mortality and morbidity among these newborns was significantly higher when compared to our whole cohort of newborns with neonatal seizures[8,14].

Since the first descriptions of this EEG pattern authors have already related it to an unfavorable outcome[25-27]. In a recently study the follow up of newborns with BS pattern was evaluated and authors observed a less unfavorable outcome in newborns with reactive BS pattern[20]; however, their group with non reactive BS had an outcome similar to our study. Holmes and Lombroso[21] have previously suggested a more favorable outcome associated to reactive BS pattern.

To establish a predictive value for BS pattern some investigators emphasize the importance of the amplitude of the electrical activity between the bursts[15,21], whereas others emphasize the duration of the interburst interval as the main criterion[19,22]. Menache and coll.[19] analyzing discontinuous EEGs observed that interburst intervals longer than 30 seconds were related to unfavorable neurological outcome and epilepsy. In our study we have not registered interburst intervals longer than 20 seconds. However, all EEGs had evident epileptogenic discharges.

Considering other EEG parameters evaluated, as all newborns from our sample had an unfavorable outcome, the statistical analysis was not able to show significant differences EEG - related.

Spreafico and coll.[30] have suggested as a possible pathophysiologic mechanism for BS pattern

impairment in apoptosis that would lead to a condition for cortical disconnection. This finding may probably explain the generation of burst-suppression in newborns with idiopathic neonatal epileptic encephalopaties. However, in cases where multiple insults have damaged specific cortical and subcortical regions as shown by Aso[24], the proposed disconnection may happen due to structural impairment.

In conclusion, the non-reactive BS pattern may appear related to many neonatal neurological disorders and is associated with early and refractory neonatal seizures. It is clearly associated with elevated morbidity and mortality and to the development of post–neonatal epilepsy.

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