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Original article

Phenobarbital for neonatal seizures: response rate and refractoriness predictors

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Abstract

Background: Phenobarbital is the first-line choice for neonatal seizures treatment, despite a response rate of approximately 45%. Failure to respond to acute anticonvulsants is associated with poor neurodevelopmental outcome but knowledge on predictors of refractoriness is limited.

Objectives: To quantify response rate to phenobarbital and to establish variables predictive of its lack of efficacy.

Methods: We retrospectively evaluated newborns with electrographically-confirmed neonatal seizures admitted between January 1999 and December 2012 to the Neonatal Intensive Care Unit of Parma University-Hospital (Italy), excluding neonates with status epilepticus. Response was categorized as complete (cessation of clinical and electrographic seizures after phenobarbital administration), partial (reduction but not cessation of electrographic seizures with the first bolus, response to the second bolus) or absent (no response after the second bolus). Multivariate analysis was used to identify independent predictors of refractoriness.

Results: Out of 91 newborns receiving phenobarbital, 57 (62.6%) responded completely, 15 (16.5%) partially and 19 (20.9%) did not respond. Seizure type ($p=.02$), background EEG ($p\leq.005$) and neurological examination ($p\leq.005$) correlated with response to phenobarbital. However EEG ($p\leq.02$) and seizure type ($p\leq.001$) were the only independent predictors.

Conclusions: Our results suggest a prominent role of neurophysiological variables (background EEG and electrographic-only seizure type) in predicting the absence of response to phenobarbital in high risk newborns.

Key words: neonatal seizures, therapy, phenobarbital, treatment outcome, refractoriness predictors, newborns.

Background

The presence of neonatal seizures (NS) is associated with increased likelihood of negative outcome, including death and long-term neurodevelopmental sequelae.[1]

Therapeutic options are still unsatisfactory,[2] as phenobarbital (still to be regarded as the the first line drug) has been reported to control NS in up to 43% of cases[3] and the use of second-generation anticonvulsant drugs is still limited due to the paucity of available evidence,[4] in spite of the significant effort in developing alternative or adjunct therapeutic strategies[5] that could improve response rates, in an attempt to improve neurodevelopmental outcome.

Various studies reported refractoriness to acute administration of antiepileptic drugs in the neonatal period to be predictive of adverse outcome[3, 6, 7] and of subsequent development of chronic epilepsy.[8, 9] While there has been growing interest in the definition of predictors of medical intractability in pediatric epilepsy,[10] factors allowing the prediction of failure to control neonatal seizures remain largely elusive.

To contribute to the understanding of predictors of refractoriness to acute phenobarbital treatment in NS, we reviewed the charts of patients seen at the Neonatal Intensive Care Unit (NICU) of our institution to quantify the percentage of newborns with electrographically-confirmed NS who failed to respond to phenobarbital to identify early clinical and instrumental findings predictive of refractoriness.

Materials and methods

We retrospectively reviewed clinical and instrumental data regarding newborns with electrographically-confirmed NS, consecutively admitted to the NICU at Parma University-Hospital

between January 1999 and December 2012 (Figure 1). Both electroclinical and electrographic-only seizures were included. We excluded newborns with a diagnosis of neonatal status epilepticus. All newborns at high risk for NS due to the presence of predisposing factors such as hypoxic-ischemic encephalopathy, sepsis, meningitis, metabolic disorders, brain malformations, intraventricular hemorrhage (IVH) or periventricular leukomalacia (PVL) on brain US scans, or with clinical signs suggestive of seizures, underwent serial EEGs during the neonatal period. Conventional polygraphic video-EEGs in our NICU were recorded by specialised personnel during day shifts from Monday to Friday, while on nights and during week-ends EEGs can be requested if urgent, but recordings are not undertaken on a regular basis. They were recorded at the bedside and, depending on infants' head size, 21 or 10 cerebral electrodes were applied according to the 10-20 International System modified for neonates. Electrocardiogram, lateral eye movements, chin electromyographic activity, and abdominal respiration were additional physiologic variables most frequently monitored. Recordings continued until a complete cycle of wakefulness, quiet and active sleep were obtained, or, if not clearly distinguishable, they continued for at least 60 minutes.

NS were defined according to electroencephalographic (EEG) criteria as ictal discharges showing a clear onset and termination, duration of at least 10 seconds and an evolution in frequency and morphology over time.[11] We collected the following clinical data: gender, gestational age, mode of delivery (spontaneous versus caesarean section), birth weight, Apgar scores at 1, 5 and 10 minutes, etiology, time of seizure onset (<48 hours of life or afterwards), seizure type, ultrasound brain scans, background EEG findings and neurological examination. These variables were scored as previously reported.[1] Background EEG findings were grouped into two categories: 1) normal or mildly abnormal in the presence of 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 when there were asymmetries in voltage or frequencies, asynchrony for age, isoelectric or low voltage invariant activity, burst suppression pattern, or

permanent discontinuous activity.[12] The first EEG in which electroclinical and/or electrographic-only seizures were recorded was used to score background activity.

Newborns were followed up with serial cranial ultrasound scans with a 7 MHz probe (Acuson Aspen). Intraventricular haemorrhage, if present, was scored according to Papile's classification,[13] whereas ischaemic lesions according to deVries[14] and ventriculomegaly according to Levene.[15] Ultrasound findings were grouped into three categories: normal; mildly abnormal: intraventricular hemorrhage (IVH) of degrees 1 or 2, transient periventricular echodensities or borderline ventricular dilatation; severely abnormal: IVH of degree 3 or 4, intraparenchymal hemorrhage, periventricular leukomalacia, and brain malformations. NS were classified as subtle, clonic (multifocal/focal), tonic (generalized, focal), and myoclonic (focal, multifocal, generalized)[16] and had to be associated with EEG changes. However, for statistical purposes, seizure types were divided as: 1) one electroclinical seizure type, 2) more than one electroclinical seizure type, 3) electrographic-only seizures. To avoid the inclusion of paroxysmal non-epileptic neonatal movements[17] we selected only electrographically-confirmed NS. The neurological examination performed before the onset of neonatal seizures was classified as follows: (i) normal/,mildly abnormal: with normal muscle tone or mild hypertonia, active muscle movements present, normal alertness for age or hyperexcitability; (ii) moderately abnormal: with hypotonia/hypertonia, decreased active muscle movements, and lethargy; and (iii) severely abnormal: flaccid, inactive, and/or coma.

We excluded newborns with neonatal status epilepticus (NSE) defined as continuous seizure activity for at least 30 minutes or recurrent seizures lasting a total of ≥30 minutes without definite return to the baseline neurological condition between seizures, in any 1-hour period (hourly seizure burden range: ≥50% - 100%).[18] Newborns with NSE were excluded from this retrospective study due to its intrinsic refractoriness to phenobarbital. Etiologies were grouped in the following 3 categories: hypoxic-ischemic encephalopathy, cerebral hemorrhage and other etiologies. Perinatal asphyxia was

defined based on the presence of an Apgar score ≤5 at 5 minutes, need for resuscitation with positive pressure ventilation and oxygen for >1 minute immediately after birth, an arterial pH ≤7.10 and a base deficit ≥14 mmol/L within the first hour after birth.[19] Hypoxic-ischaemic encephalopathy was defined and scored according to Sarnat and Sarnat.[20] Within the group labeled as "other etiologies" we included cases of cerebral malformation, inherited metabolic disorder, transient metabolic disorder (e.g. hypocalcemia, hypoglycemia, uremia), central nervous system infection/sepsis and unknown etiology.

Ethics, consent and permissions

Informed consent to use of patients' clinical data for research purpose was obtained from parents in accordance with ethics policy of our Institution, which approved the study. Written informed consent forms were stored in each patient's hospital chart.

Treatment protocol for NS in our Unit

The therapeutic protocol used in our Unit during study period was as follows: intravenous (IV) bolus of phenobarbital at a dose of 20 mg/kg, repeated once if seizures persist 15 minutes after bolus has been completed, followed by IV administration of phenytoin at a loading dose of 20 mg/kg at a rate of no more than 1 mg/kg/minute for persisting seizures. If seizures persisted in spite of this treatment, our third-line anticonvulsant was an IV bolus of midazolam at 0.15 mg/kg followed by continuous IV infusion at 1 μg/kg/minute, increased by 1 μg/kg/minute every 15 minutes.[1] In some instances, IV diazepam was administered as either the second or third-line choice, at a dose of 0.2-0.5 mg/kg. However, the neonatologists in charge decided the therapy according to the clinical context (Figure 2).

Response to phenobarbital therapy classification.

We classified patients' response to phenobarbital administration as follows: 0= complete response to the first phenobarbital bolus; 1= partial response, corresponding to reduction but not cessation of electrographic seizures with the first bolus and response to the second bolus, 2= no seizure reduction with the second bolus of phenobarbital.

Statistical analysis

Nominal data were analyzed by means of the $\chi 2$ test or Fisher's exact test as appropriate.
Odds ratio (OR) was calculated using a univariate logistic regression model to determine which independent variable(s) were related to refractoriness to phenobarbital. Variables with a *p* value <0.05 and with an OR>1 on univariate analysis were accepted as significant and included in a multiple logistic regression analysis used to evaluate which independent variable/s were related to failure to respond to phenobarbital.
Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Version 21; IBM SPSS Statistics for Windows, Armonk, NY, 2012).

Results

From the total cohort of 154 newborns who had electrographically-confirmed NS, we excluded 47 cases with NSE (28 full-term and 19 preterm neonates), thus identifying 107 newborns, of whom 50 were born at term and 57 were preterm neonates. Sixteen patients did not receive phenobarbital (16/107=15%), 11 of which were born preterm. Four neonates exclusively received an etiological therapy: one full-term was administered pyridoxine and one calcium, whereas two preterm neonates received IV glucose.

The remaining 91 newborns (55 males), 45 (49.5%) born at term and 46 (50.5%) preterm were included in the analysis. Detailed patients' characteristics are shown in Table 1.

Seizure semiology: a total of five newborns had exclusively electrographic seizures. Two showed a complete response and three a partial response to phenobarbital. Seizure semiology in newborns with electroclinical seizures is depicted in Figure 3. Data are divided according to the number of different seizure types presented by each newborn in: **one seizure type and more than one seizure type. In this second group, if clonic seizures were present, then the newborn was classified as presenting with clonic seizures, while when different seizure types were present, we classified patients according to their prevailing seizure type into: myoclonic, tonic, or subtle.**

Etiologies in our cohort were distributed as follows: 45 patients had hypoxic-ischemic encephalopathy (29 showed a complete response to phenobarbital, 9 a partial response, 7 no response); 21 had a cerebral hemorrhage (14 showed a complete response to phenobarbital, 2 a partial response, 5 no response); 25 had other etiologies: 4 had a cerebral malformation, 3 an inherited metabolic disorder, 9 had a transient metabolic disorder, 4 had a central nervous system infection/sepsis, one had a syndromic diagnosis, in 4 this was unknown. Of these, 14 showed a complete response to phenobarbital, 4 a partial response, 7 no response. The distribution of response categories did not significantly differ according to etiology (p=0.653).

The number of newborns receiving only phenobarbital was 34 among full—term newborns (34/50=68%) and 40 (40/57= 70.2%) among preterm newborns.

Response to phenobarbital

Of the 91 newborns being treated with phenobarbital, 57 showed a complete response (62.6%), 15 (16.5%) a partial response and 19 (20.9%) no response.

Among examined variables, seizure type (p=.02), background EEG (p≤.005) and neurological examination (p≤.005) correlated with response to phenobarbital. The multiple logistic regression analysis, however, showed that EEG (p≤.02) and seizure type (p≤.001) were the best and only

significant independent predictors (Table 2), whereas neurological examination did not predict significantly the outcome "no response". **We also represented the results of our statistical analysis as a mosaic plot, in which the width of each different area is proportional to the number of observed cases in each cell (Figure 4).**

After the exclusion of neonates with NSE, we found a complete response in 57 subjects (62.6%), a partial response in 15 (16.5%) and the absence of response in 19 subjects (20.9%), therefore a higher response rate than reported in previous studies (33 to 45%),[3, 21, 22] possibly related to the exclusion of NSE cases from our cohort. When considering complete and partial responders together, these correspond to 79.1% of patients in our study, which would be comparable to 80% of cases with either complete cessation or substantial improvement already reported.[3] In spite of the raising concerns on its potentially neurotoxic effects,[23] phenobarbital is still the first choice drug in neonates with seizures,[24, 25] due to longer clinical experience and the inclusion in randomized controlled trials.

Factors predicting response to anticonvulsants have been seldom investigated in the neonatal period. In the pediatric epilepsy literature, predictors of medical intractability have been identified, among the others, in the presence of neuroimaging abnormalities, status epilepticus, mixed seizure types, focal slowing and symptomatic etiology.[10]

In this study, only background EEG activity ($p \leq .02$) and seizure type ($p < .001$) were confirmed as independent predictors of refractoriness. The association between abnormal background EEG and lack of response to phenobarbital was already described by Boylan et al.,[26, 27] even though the small sample size did not allow inferential statistical analysis. Furthermore, a tendency for responders to show normal or only mildly abnormal EEG background has been reported.[28] As background EEG represents one of the major prognostic factors in the context of NS,[29] it is likely that its role as a

predictor of response to therapy identifies severely affected newborns, as already concluded by others.[30]

The second predictor of lack of response to phenobarbital was the presence of electrographic-only versus one or more electroclinical seizure types. It is still debated whether all NS (electrographic as well as electroclinical) should be treated,[31, 32] even if evidence has been gathered on a correlation between electrographic-only seizures and unfavorable neurological outcome.[33] In a randomized controlled study on treatment of NS in full-term newborns with moderate-to-severe hypoxic-ischemic encephalopathy, a trend towards a shorter seizure duration in the group treated for both clinical and subclinical events was found, which was also related to prompter and more appropriate administration of anticonvulsants.[34] Our results suggest a potential need for an intensification of our surveillance strategies in high risk newborns, in order to enable clinicians to detect neonatal seizures even if subclinical and to correctly estimate their overall burden, because our data seem to confirm a detrimental role for electrographic-only seizures. On the other hand, it is important to emphasize that we did not analyze whether the presence of electrographic-only seizures identified the most severely affected or the younger preterm newborns in our cohort, which might provide an alternative explanation to our findings.

Interestingly, we found that the severity of ultrasound scan findings did not predict refractoriness to phenobarbital. This might be partially due to methodological limitations of this technique to fully assess a contributory role of brain damage in refractoriness to therapy. Alternatively, our finding could be interpreted as suggestive of a stronger contribution of functional changes, reflected by moderately or severely abnormal EEG activity, on response to medications. This seems to be further supported by the absence of a correlation between etiology and absence of a response to phenobarbital in our cohort, although it must be acknowledged that our results might also reflect the inclusion of heterogeneous conditions in our third group of etiologies for statistical reasons. This

hypothesis would be in agreement with studies in the paediatric age, identifying structural lesions as a cause of epilepsy refractoriness.[10]

In our cohort, we found a low percentage of neonates with transient metabolic derangements, such as hypoglycaemia or hypocalcaemia, who readily responded to etiological therapy. Transient metabolic derangements as a cause of NS are known to have significantly decreased over the last decades.[35] In this cohort, 54/107 (50.5%) of seizing neonates had a moderately to severely abnormal neurological examination at onset and 85/107 (79.4%) had moderate-to-severe cranial ultrasound abnormalities, reflecting higher rates of acute symptomatic seizures deriving from intraventricular hemorrhage.

One potential limitation is that plasma levels of phenobarbital were not routinely obtained in all patients, since therapeutic decisions were usually necessary before plasma level results could be available. Nevertheless, blood concentration of phenobarbital is highly variable in neonates[36] due to its pharmacokinetic properties including the variability of plasma protein binding in newborns limits the value of estimates of total concentration.

In summary, this study reports on the response rate to phenobarbital in newborns with electrographically-confirmed NS, excluding neonates with NSE. We identified background EEG and the presence of electrographic-only seizures as predictors of refractoriness to phenobarbital therapy.

Our findings suggest that refractoriness to phenobarbital can be predicted on the basis of background EEG and seizure type findings. Identification of early predictors of phenobarbital refractoriness might represent a useful research field, providing neonatologists and pediatric neurologists with early and readily available clinical tools potentially impacting on quick decision-making. The negative effect of electrographic-only seizures on response to phenobarbital also suggests a need for close EEG surveillance of high risk newborns.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article. All the authors are responsible for reported research and have participated in the concept and design; analysis and interpretation of data; drafting or revising of the manuscript, and they have approved the manuscript as submitted. There are no financial disclosures. The manuscript does not report results of a clinical trial. This study is not industry-sponsored.

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Tables titles and legends

Table 1. Clinical, neurophysiological and neuroradiological data and their association with response to phenobarbital.

List of abbreviatons: n: number, %: percentage, CI: confidence interval, GA: gestational age, BW: birth weight, g: grams, min: minutes, HIE: hypoxic-ischaemic encephalopathies, h: hours, CrUSS: cranial ultrasound scan, EEG: electroencephalogram, CruSS I: normal, CrUss II: mildly abnormal, CrUss III: severely abnormal.

Table 2. Predictors of non-responsiveness to phenobarbital.

List of abbreviations. CI: confidence interval; EEG: elctroencephalogram; EEG I: normal/mildy abnormal; seizure type 1: one electroclinical seizure type; seizure type 2: more than one electroclinical seizure type; OR: odds ratio.

Figure legends

Figure 1. Study methods. BW: birth weight; CrUSS: cranial ultrasound scan; EEG: electroencephalogram; GA: gestational age; HIE: hypoxic-ischaemic encephalopathy; hrs: hours; IVH: intraventricular haemorrhage; NICU: neonatal intensive care unit; NS: neonatal seizures; PB: phenobarbital.

Figure 2. Therapeutical protocol in our Unit at the time of the study. EEG: electroencephalogram; IV: intravenous; kg: kilogram; MDZ: midazolam; mg: milligram; min: minute; µg: microgram; NS: neonatal seizures; PB: phenobarbital; PHT: phenytoin.

Figure 3. Distribution of different electroclinical seizure types in our cohort, divided according to response to phenobarbital (complete response, partial response or no response) and gestational age (preterm versus full-term newborns). Figure 3A shows the distribution of different electroclinical

seizure types in newborns with only one seizure type, **figure 3B shows different combinations of electroclinical seizures in newborns with more than 1 seizure type. If clonic seizures are present, the patient is classified as "prevailing clonic", while for other seizure types, each newborn is classified according to the main seizure type into myoclonic, tonic or subtle.**

Figure 4. The mosaic plot allows to examine the relationship among two or more categorical variables. The horizontal bar widths are proportional to the conditional probability associated to each categorical variable: response to the phenobarbital (response: white, partial response: light gray, no response: dark gray), EEG (normal/mildly abnormal: diagonal pattern, moderately/severely abnormal: horizontal pattern) and seizure type (more than one seizure type: thin edge, one seizure type: medium edge, electrographic-only: large edge).

List of abbreviatons: C: clonic, fC: focal clonic, E: electrographic, FT: full-term newborn, M: myoclonic, mC: multifocal clonic, Part Resp.: partial responder, PT: preterm newborn, Resp.: Responder, S: subtle, T: tonic.

Variables	All n (%)	Response to phenobarbital, n (%) Response	Partial response	No response	P	Odd Ratio	95%CI	p
Delivery					.5			
Spontaneous	41 (45.5)	24 (58.5)	9 (21.9)	8 (19.5)				
Caesarean Section	50 (55.5)	33 (66)	6 (12)	11 (22)				
GA					.5			
≥37	45 (49.5)	28 (62.2)	9 (20)	8 (17.8)				
30-36	17 (18.7)	10 (58.8)	4 (23.5)	3 (17.7)				
≤29	29 (31.8)	19 (65.5)	2 (6.9)	8 (27.6)				
BW					.3			
≥2500g	48 (52.7)	31 (64.6)	8 (16.6)	9 (1.8)				
1500-2499g	10 (10.9)	5 (50)	4 (40)	1 (10)				
1000-1499g	12 (13.2)	8 (66.6)	2 (16.7)	2 (16.7)				
<1000g	21 (23.1)	13 (61.9)	1 (4.8)	7 (33.3)				
1 min Apgar score					.1			
8-10	36 (39.6)	26 (72.2)	7 (19.5)	3 (8.3)				
4-7	23 25.3)	15 (65.2)	3 (13.1)	5 (21.7)				
0-3	32 (35.2)	16 (50)	5 (15.6)	11 (34.6)				
5 min Apgar score					.43			
8-10	47 (51.6)	31 (66)	8 (17)	8 (17)				
4-7	31 (34.1)	20 (64.5)	3 (9.7)	8 (25.8)				
0-3	13 (14.3)	6 (46.1)	4 (30.8)	3 (23.1)				
10 min Apgar score					.1			
8-10	67 (73.6)	46 (68.7)	10 (14.9)	11 (16.4)				
≤7	24 (26.4)	11 (45.9)	5 (20.8)	8 (33.3)				
Etiology					.7			
HIE	45 (49.4)	29 (64.4)	9 (20)	7 (15.6)				
Cerebral Haemorrhage	21 (23.1)	14 (66.7)	2 (9.5)	5 (23.8)				
Others	25 (27.5)	14 (56)	4 (16)	7 (28)				
Seizure onset					.9			
≤48 h	30 (32.9)	18 (60)	6 (20)	6 (20)				
>48 h	61 (67)	39 (63.9)	9 (14.8)	13 (21.3)				
CrUSS					.3			
I	17 (18.7)	12 (70.6)	4 (23.5)	1 (5.9)				
II	35 (38.5)	24 (68.6)	5 (14.3)	6 (17.1)				
III	39 (42.8)	21 (53.8)	6 (15.4)	12 (30.8)				
Seizure type					*.07*			
1 type	30 (32.9)	19 (63.3)	3 (10)	8 (26.7)		1		
> 1 type	56 (61.5)	36(64.3)	9 (16.1)	11 (19.6)		.92[a] 1.27[b]	.68-1.23[a] .58-2.76[b]	 .02[b]
Electrographic-only	5 (5.5)	2 (40)	3 (60)	0[c]				
EEG					**.000**			
Normal/mildly abnormal	40 (43.9)	32 (80)	7 (17.5)	1 (2.5)		1		
Moderately/severely abnormal	51 (56.1)	25 (49)	8 (15.7)	18 (35.3)		1.67[a] 2.84[b]	1.29 – 2.17[a] 1.51-5.36[b]	.001 .005
Neurological examination					**.03**			
Normal/mildly abnormal	45 (49.4)	30 (66.7)	10 (22.2)	5 (11.1)		1		
Moderately abnormal	32 (35.2)	21 (65.6)	4 (12.5)	7 (21.9)		1.14[a] 1.83[b]	.89-1.4[a] .78-3.34[a]	.002 .005
Severely abnormal	14 (15.4)	6 (42.9)	1 (7.1)	7 (50)		1.86[a] 5.3[b]	1.1-3.39[a] .82-4.53[b]	.001 .0

[a]: response cohort; [b]: partial response cohort; [c] OR not evaluable

		OR	95% CI	p
Response	*Intercept*			*.000*
	Normal / mildly abnormal EEG	19.14	2.30-159.29	.006
	Seizure: one type	.002	.00017-.0022	.000
Partial response	*Intercept*			*.000*
	Normal / mildly abnormal EEG	16.74	1.57-177.82	.02
	Seizure: one type	.001	.00039-.0023	.000

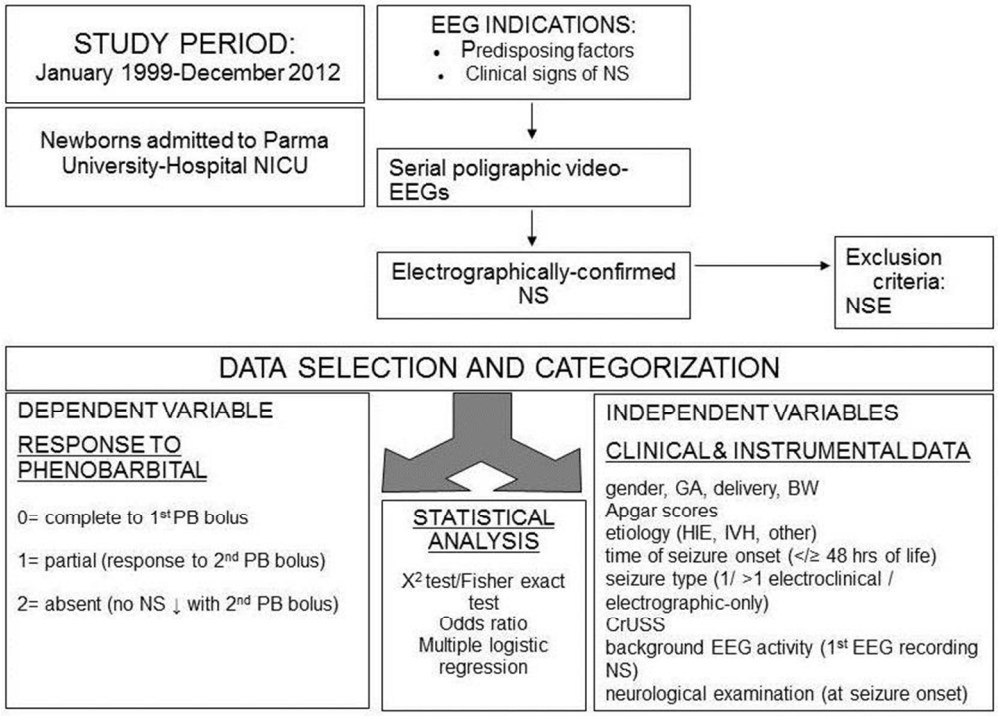

Figure 1. Study methods. BW: birth weight; CrUSS: cranial ultrasound scan; EEG: electroencephalogram; GA: gestational age; HIE: hypoxic-ischaemic encephalopathy; hrs: hours; IVH: intraventricular haemorrhage; NICU: neonatal intensive care unit; NS: neonatal seizures; PB: phenobarbital.
70x51mm (300 x 300 DPI)

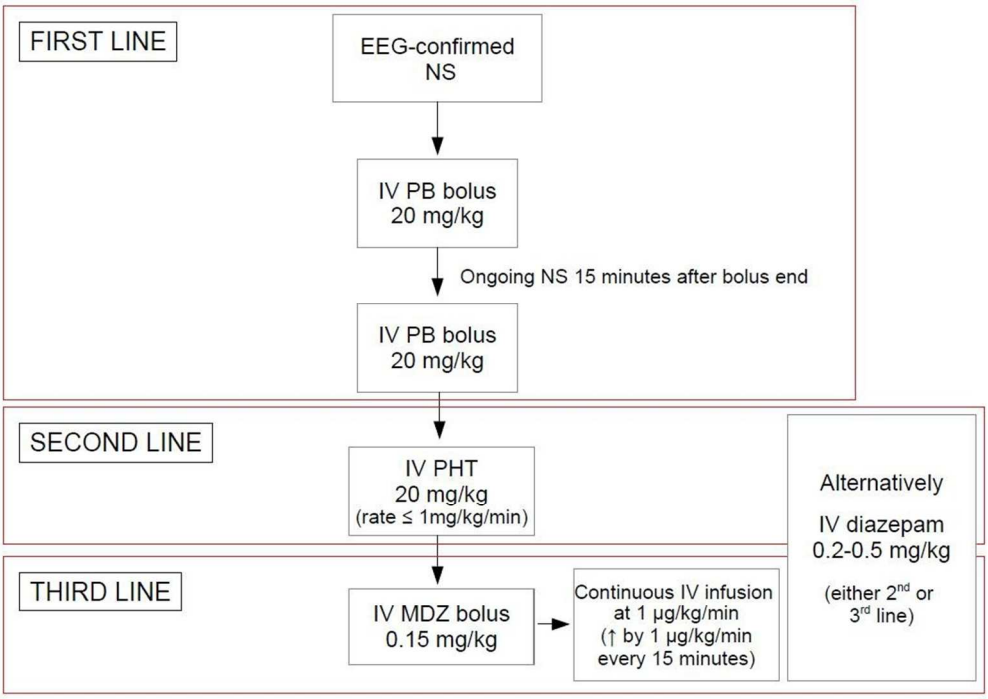

Figure 2. Therapeutical protocol in our Unit at the time of the study. EEG: electroencephalogram; IV: intravenous; kg: kilogram; MDZ: midazolam; mg: milligram; min: minute; µg: microgram; NS: neonatal seizures; PB: phenobarbital; PHT: phenytoin.
90x63mm (300 x 300 DPI)

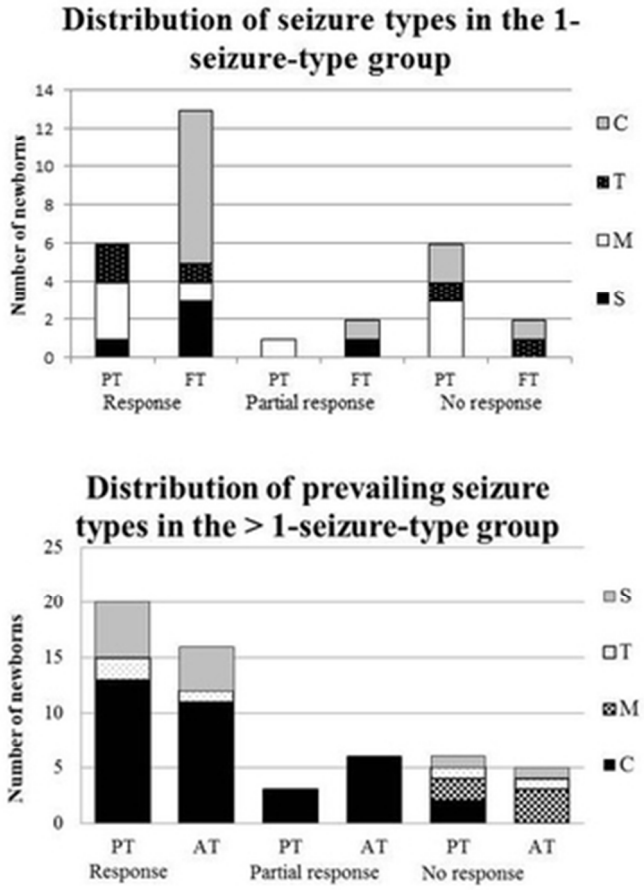

Figure 3. Distribution of different electroclinical seizure types in our cohort, divided according to response to phenobarbital (complete response, partial response or no response) and gestational age (preterm versus full-term newborns). Figure 3A shows the distribution of different electroclinical seizure types in newborns with only one seizure type, figure 3B shows different combinations of electroclinical seizures in newborns with more than 1 seizure type. If clonic seizures are present, the patient is classified as "prevailing clonic", while for other seizure types, each newborn is classified according to the main seizure type into myoclonic, tonic or subtle.
28x38mm (300 x 300 DPI)

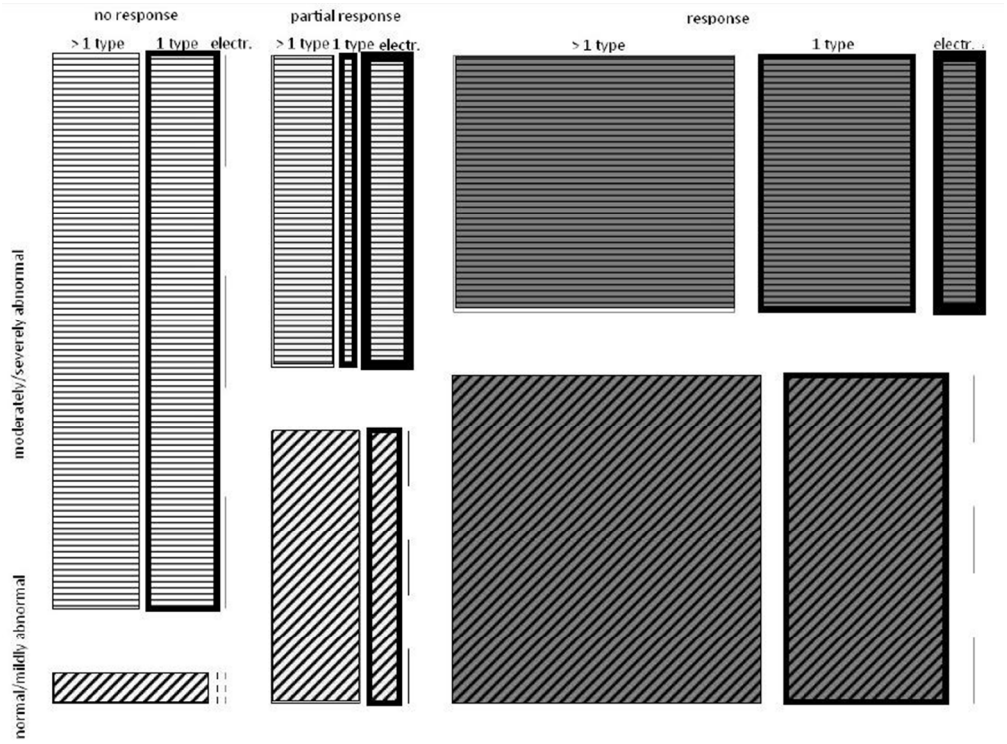

Figure 4. The mosaic plot allows to examine the relationship among two or more categorical variables. The horizontal bar widths are proportional to the conditional probability associated to each categorical variable: response to the phenobarbital (response: white, partial response: light gray, no response: dark gray), EEG (normal/mildly abnormal: diagonal pattern, moderately/severely abnormal: horizontal pattern) and seizure type (more than one seizure type: thin edge, one seizure type: medium edge, electrographic-only: large edge).

List of abbreviatons: C: clonic, fC: focal clonic, E: electrographic, FT: full-term newborn, M: myoclonic, mC: multifocal clonic, Part Resp.: partial responder, PT: preterm newborn, Resp.: Responder, S: subtle, T: tonic.

73x54mm (300 x 300 DPI)