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Original article

Influence of etiology on treatment choices for neonatal seizures: A survey among pediatric neurologists

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Abstract

Background: A targeted treatment approach is increasingly promoted in epilepsy management.

Aim: To investigate if etiology (both established or initially presumed) influences antiepileptic drug choice of experts in neonatal seizures.

Methods: An invitation to participate to a web-based questionnaire was sent to Italian pediatric neurologists affiliated to the Italian Society of Pediatric Neurology (SINP).

Results: 19 pediatric neurologists from different centers, all consultants of third level Neonatal Intensive Care Units (NICUs) answered. As first-line drug phenobarbital was the most common choice, it was used in 79% of cases of acute symptomatic seizures, in 63% of structural epilepsy, in 42% of genetic epilepsies. As second-line drug phenytoin was used by 58% in acute symptomatic seizures, 37% in structural epilepsy, 5% in genetic epilepsy. Pyridoxine/pyridoxalphosphate was much more used in genetic epilepsy (as first-line in 26%, as second-line in 37%) than in the other two conditions.

Long-term conventional EEG monitoring was suggested as important to verify efficacy of drugs in controlling seizures by 84% of interviewed neurologists, but EEG was available around the clock in only 53% of their centers. 1 to 3-channel aEEG/EEG (commonly named CFM) was often used instead of conventional EEG monitoring.

Conclusion: This is the first survey looking at a targeted approach in treatment of neonatal seizures by pediatric neurologists consulted by NICUs. The treatment approach is similar to previous surveys in case of acute symptomatic seizures, but in case of other etiologies the choices are different, especially for the second-line option. Larger studies should address this topic.

Keywords: Neonatal seizures; Survey; Targeted therapy; Antiepileptic drugs; EEG; aEEG

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1. Introduction

In the last years the etiological diagnosis of neonatal seizures is increasingly more common at earlier stages as a consequence of greater scientific knowledge and early availability of neuroimaging, neurophysiology and laboratory data, as metabolic and genetic tests. The role of a targeted treatment or precision medicine in neonatal seizures based on etiology both established or presumed according to the initial clinical and instrumental features, although still a challenging task at the onset of seizures, is becoming increasingly supported by research data in the last years [1–3].

Phenobarbital (PB) or phenytoin (PHT) are still the preferred first option antiepileptic drugs (AEDs) in neonatal seizures [4,5], although there are concerns about their potential neurotoxicity on the developing brain [6]. Among the new AEDs, levetiracetam (LEV) appears as the most promising [7]. In the last years vitamins (pyridoxine and pyridoxalphophate) are increasingly used when the possibility of vitamin dependent epilepsy is suspected [8]. There is now evidence that some genetic neonatal epilepsies or neonatal onset epileptic encephalopathies respond better or selectively to certain drugs, as sodium channel blockers in KCNQ2 or SCN2A related epilepsies [1]. Thanks to recent scientific advances, epilepsy experts can now sometimes hypothesize the most probable diagnosis based on clinical phenotype, EEG and imaging features [1]. In some cases the antiepileptic treatment can be better and earlier targeted on the base of presumed etiology. This is particularly useful when neonatal seizures are refractory to the first-line AED.

However, at present evidence-based data on neonatal seizure management are still limited, and internationally agreed advanced guidelines are still needed [4] particularly considering the issue of treatment approach targeted on etiology at early stages.

Herein authors aim to study if established or presumed etiology is currently influencing AED choices in the treatment of neonatal seizures among experts in neonatal seizures, using a web-based questionnaire [9].

2. Materials and methods

2.1. Study design

A web-based questionnaire was sent to pediatric neurologists members of the Italian Paediatric Neurology Society (SINP) using a survey tool available online (https://docs.google.com/forms) in 2016. The respondent physicians had to be experts in neonatal epilepsy and involved by neonatologists of third-level Neonatal Intensive Care Units (NICU) in decision-making management of neonatal seizures.

2.2. Study questionnaires

The Web-based questionnaire included questions addressing current clinical practices. The questionnaire was divided into three sections:

1) Demographic data of participants;
2) Treatment practices, including first-, second-, third-, fourth antiepileptic drug choice. Neonatal seizures were classified according to traditional ILAE classifications [10] in three categories as established or presumed at the moment of treatment in: a) acute symptomatic seizures; b) structural epilepsy; c) genetic epilepsy;
3) Neurophysiological monitoring modalities used to verify AEDs efficacy.

In addition to understand in which proportion the AED preference of pediatric neurologists influences AED choice in the clinical practice since the first AED choice, it was asked if in the participant center the first AED choice was a choice of the neonatologist, the pediatric neurologist or a shared choice.

3. Results

3.1. Web-based questionnaire for experts in neonatal seizures

3.1.1. Respondents' features

19 pediatric neurologists working for different third level NICUs (corresponding to 17% of third-level NICUs across Italy) answered.

The average age of the 19 respondents was 53 years (SD 9.6 years, range: 37–68 years).

All participant answered to all questions, indicating the AED that they would use for the first, second, third and fourth AED choice. The physician doing the first line AED choice in the participant centers was indicated as follows: for 48% it was a shared decision between neonatologist and neurologist, whereas for 26% it was a decision of the neonatologist alone and for 26% a decision of the neurologist alone (so in 74% of respondent centers neurologists contributed to the AED choice since the first AED).

3.1.2. AED options (see Table 1)

3.1.2.1. First option AED. PB was indicated as the most common first-line AED for neonatal seizures, but the percentage differed for the three etiological categories as follows: 79% for acute symptomatic seizures, 63% for structural epilepsy and 42% for genetic epilepsy. Vitamins (pyridoxine or pyridoxalphosphate) were the first-line AED for 26% of respondents only in case of a presumed genetic epilepsy and for none in the other two seizure categories.

3.1.2.2. Second option AED. PHT was chosen as second-line AED by 58% of participants in case of acute symptomatic seizures, 37% in case of structural epilepsy, and by only 5% in case of genetic epilepsy, in whom conversely vitamins were indicated by 37% of respondents.

3.1.2.3. Third option AED. Midazolam was the most used third-line treatment, as it was indicated by 42% of participants in case of acute symptomatic epilepsies, but only by 26% in case of structural epilepsy and 3% in case of genetic epilepsy.

3.1.2.4. Fourth choice AED. The choices were significantly different among participants in all neonatal seizures.

3.1.2.5. Additional information about AED choices. 4 of 19 participants (21%) declared that in rare neonatal cases AED choice depended not only on etiology, but on the type of seizures in case of peculiar ictal semiology (indicating for instance as vigabatrin was early preferred in case of tonic epileptic spasms in Ohtahara syndrome).

3.1.3. Neurophysiological monitoring

Continuous conventional EEG together with a simplified trend monitoring modality (usually aEEG) was indicated as the ideal monitoring option to verify AED efficacy on neonatal seizures by 84% of pediatric neurologists, whereas 16% of them indicated the use of conventional EEG of standard duration (around 60–90 min) in consecutive days, completed with continuous CFM (Cerebral Function Monitoring), a simplified monitoring system with only 1 to 3 EEG/aEEG channels for 24–48 h, as a sufficient monitoring.

Availability to perform conventional EEG at any hour around the clock (with technician, neurophysiologist and equipment available) was indicated in only 53% of respondent centers.

4. Discussion

As previous surveys have shown, the present survey on neonatal seizures confirms that PB remains the most commonly used first-line AED for neonatal seizures [4,11,12].

Unlike previous surveys on neonatal seizures [4], in this study we investigated specifically the influence of etiology on AED choice instead of general AED use in neonatal seizures taken all together, focusing our study on the population of physicians expert in neonatal seizure management consulted by NICUs. Among the studied sample of Italian pediatric neurologists the most commonly suggested sequence of AED choices from the first to the fourth choice in case of acute symptomatic seizures was the following: PB (79%), PHT (58%), midazolam (MDZ) (42%), LEV (42%). Conversely in neonatal seizures due to a genetic epilepsy or structural epilepsy, AED choice concordance among pediatric neurologists was lower than in acute symptomatic seizures, probably as consequence of the fact that in these situations therapeutic choices are less standardized and depends on the specific clinical situation (Table 1). Interestingly only in case of a presumed genetic epilepsy an early therapeutic trial of vitamins was early considered (as first-line 26%, as second-line 37%, as third-line 16%), so that in genetic epilepsy vitamins are considered by 79% of interviewed neurologists in the first three options. MDZ was the third-line option in case of acute symptomatic seizures, but not in case of structural epilepsy or genetic epilepsy, probably because it is considered a short-acting therapy suitable for situations supposed to be transitory. This survey confirms also the tendency to the increasing off-label use of LEV [13], probably due the recent several studies on its good efficacy and safety profile in neonatal seizures and to the open debate about the neurotoxic effects of the old AEDs in the developing brain [6,7].

One limitation of the present study is the lack of data treatment choices of the neonatologists, therefore we could not compare neurological and neonatological management of neonatal seizures. However, comparing results of the present study with existing data in the literature addressing treatment options of neonatologists and neurologist in neonatal seizures [11,12], we found that in previously published studies the pharmacological approach indicated by neonatologists for neonatal seizures was very similar to the approach adopted by the present sample of pediatric neurologists for the category of acute symptomatic seizures (PB around 80% in both interviewed samples). By contrast, it is very different if compared to the approach of pediatric neurologists in case of neonatal seizures in the context of structural epilepsy or genetic epilepsy, where the percentage of PB preference is lower, with differences becoming bigger in the second-line treatment, where a vitamin trial peaks to 37% only in case of a presumed genetic epilepsy.

These data show that a targeted treatment approach based on etiology of neonatal seizures is already currently considered in the clinical practice by pediatric neurologists. Consequently, it is possible to infer that, especially in situations different from acute symptomatic seizures, an early consultation with a specialist may be useful in better targeting the treatment, with the aim of improving the seizures control, particularly when seizures persist after the first-line AED and are not symptomatic of an acute injury. An etiology-based approach to treatment (“precision medicine”) should be promoted among all physicians involved in the care of neonates with seizures with the help of shared guidelines.

Table 1
AED option (first, second, third, fourth AED) in neonatal seizures according to the survey conducted on experts on neonatal seizures working for 19 third level NICU. N, number of respondents; %, percentage of respondents; ASS, acute symptomatic seizures; SE, structural epilepsy; GE, genetic epilepsy; PB, phenobarbital; PHT, phenytoin; MDZ, midazolam; LEV, levetiracetam; Pyr/PLP, pyridoxine/pyridoxal-phosphate; VPA, valproic acid; GVG, vigabatrin; TPM, topiramate; CBZ, carbamazepine; Others, other AED (as lidocaine, thiopental, benzodiazepines different from midazolam or other unspecified AED).

	First AED			Second AED			Third AED			Fourth AED		
	ASS	SE	GE	ASS	SE	GE	ASS	SE	GE	ASS	SE	GE
AED	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
PB	15 (79)	12 (63)	8 (42)	2 (11)	4 (21)	1 (5)	1 (5)	1 (5)	4 (21)	1 (5)	1 (5)	2 (11)
PHT	1 (5)	3 (16)	2 (11)	11 (58)	7 (37)	1 (5)	4 (21)	2 (11)	4 (21)	2 (11)	3 (16)	3 (16)
MDZ	1 (5)	0 (0)	0 (0)	4 (21)	2 (11)	4 (21)	8 (42)	5 (26)	3 (16)	2 (11)	1 (5)	2 (11)
LEV	2 (11)	3 (16)	2 (11)	0 (9)	4 (21)	5 (26)	4 (21)	4 (21)	2 (11)	8 (42)	2 (11)	5 (26)
Pyr/PLP	0 (0)	0 (0)	5 (26)	1 (5)	0 (0)	7 (37)	2 (11)	1 (5)	3 (16)	1 (5)	3 (16)	2 (11)
VPA	0 (0)	1 (5)	1 (5)	1 (5)	1 (5)	1 (5)	0 (0)	0 (0)	1 (5)	2 (11)	1 (5)	0 (0)
GVG	0 (0)	0 (0)	1 (5)	0 (0)	1 (5)	0 (0)	0 (0)	2 (11)	2 (11)	0 (0)	4 (21)	1 (5)
TPM	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	0 (0)	2 (11)	2 (11)	2 (11)
CBZ	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	3 (16)	0 (0)	0 (0)	0 (0)	1 (5)
Others	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (5)	2 (11)	1 (5)
Total	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)	19 (100)

In addition, on the base of the survey results on the neurophysiological monitoring of neonatal seizures, we confirmed the current broad use of CFM (1 to 3 channel-EEG/aEEG) in third level NICU, although conventional EEG is still considered by pediatric neurologists the gold standard for diagnosis of epilepsy and monitoring of seizures in neonates and CFM is considered an instrument with many limits. This contrast (CFM versus conventional EEG) is easily explained by the fact that the conventional EEG is available around the clock only in some NICUs. As conventional EEG requires major expertise, CFM at present seems to respond to the neonatologist demand of having an easy instrument to monitor seizures and brain function around the clock despite its known limitations. In future this neurophysiological approach could change with technological advances.

In our experience the web-based survey was an easy and useful instrument to evaluate clinical practice, even if the low rate of participation remains a problem that should be better addressed. Indeed the main limitation of the present study was the limited number of respondents. However, scientific and clinical interest on neonatal seizures is growing in Italy also through the experience of the present study. An inter-societies group including members interested in neonatal neurology and neonatal seizures is being built up within Italian Society of Pediatric Neurology (SINP), Italian League Against Epilepsy (LICE), Italian Society of Neonatology (SIN).

Findings of the present study should be explored in larger international surveys and an international network on neonatal seizures among neonatologist and neurologists should be built to better address these practical issues.

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