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Epileptic Disorders

ORIGINAL ARTICLE

ILAE neonatal seizure framework to aide in determining etiology

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Abstract

Objective: To employ the neonatal seizure framework developed by the International League Against Epilepsy (ILAE) Neonatal Task force to assess its usefulness in determining the etiology of neonatal seizures.

Methods: The members of the ILAE Neonatal Task Force evaluated 157 seizures from 146 neonates to determine internal validity and associations between semiology and a specific etiology.

Results: Provoked neonatal electrographic and electroclinical seizures were due to multiple etiologies. For electroclinical seizures, unilateral clonic seizures were typically seen with vascular etiologies, focal tonic seizures and sequential seizures with genetic etiologies, and myoclonic seizures with inborn errors of metabolism. Electrographic seizures were often seen in hypoxic–ischemic encephalopathy or vascular etiologies.

Significance: These data suggest that the ILAE neonatal seizure classification may be used as a bedside tool to aid and guide workup to determine the etiology of seizures.

KEYWORDS

classification, etiology, neonatal seizure, semiology

This work is original and has not been presented at a meeting or in another publication.

1 | INTRODUCTION

Seizures are common in the neonatal period and are often an acute response to a prenatal or perinatal insult. Acute provoked seizures are often due to an identifiable and possibly treatable etiology and are not considered epilepsy. While the majority of neonatal seizures are provoked by an acute insult, neonatal epilepsy syndromes can occur and are typically due to a pathogenic variant. Seizures can present with different clinical characteristics and at specific times depending on the underlying cause.[1] Seizures in neonates are often the first manifestation of brain dysfunction. Early recognition and identification can aid in rapid diagnosis and treatment. The International League Against Epilepsy (ILAE) neonatal classification provides a common language to classify seizures.[2]

In 2014, the ILAE Task Force on Neonatal Seizures was tasked to create a diagnostic framework of neonatal seizures.[3] The neonatal framework uses the same categories and terminology of the previously published ILAE seizure classification,[4,5] but is (a) adapted for neonates and (b) developed to emphasize the role of electroencephalography (EEG) or amplitude-integrated EEG (aEEG) in diagnosis.[3] The usefulness of the classification in determining etiology was tested in this paper.

Key points

- Clonic seizures were often associated with a vascular etiology.
- Tonic and sequential seizures were often associated with a genetic etiology.
- Myoclonic seizures were often associated with a metabolic etiology.
- Electrographic seizures were often associated with HIE or vascular etiologies.

2 | INTERNAL EVALUATION OF THE PROPOSAL

Prior to publication of the neonatal seizure classification, the neonatal task force members met for a 2-day face-to-face session to evaluate the ease of use and practicality of the proposed classification and framework by reviewing video-EEG data of neonatal seizures of variable blinded etiologies. The primary aim was to identify the number of seizures that could not be classified ("unclassified") according to the proposal; the secondary aim was to correlate clinical seizure types to their etiologies.

3 | METHODS OF DATA REVIEW

The videos were gathered from available data of EEG-confirmed seizures from individual institutions and were sorted based on etiology. The reviewers were then blinded to the etiology and only were asked to rate the predominant clinical seizure type. Inclusion criteria for data collection were as follows: (1) randomly selected deidentified teaching and/or other clinical cases that fulfilled the predetermined etiology categories from neonatal intensive care units at Albert Einstein College of Medicine, New York (USA), Baylor College of Medicine (Texas Children's Hospital), Houston (USA), University of California San Francisco (USA), Helsinki University Central Hospital (Finland), PUCRS School of Medicine, Porto Alegre (Brazil), UCL-Institute of Child Health, London (UK) and Royal Hospital for Children Glasgow (UK) and (2) adequate EEG and video quality to verify ictal events and to review the semiology of the unobstructed whole baby. The video EEGs included both neonatal and full montages, and all the members of the committee had to agree that it was a seizure on the EEG before the semiology was reviewed.

To represent diversity as well as the common etiologies, the task force included a minimum of 30 cases with hypoxic–ischemic encephalopathy (HIE), 20 with vascular (stroke or hemorrhage), 20 with infectious causes, 20 with inborn errors of metabolism or acute metabolic disorders, 20 with pathogenic variants, and 10 with cortical malformations. There was a recognized selection bias as most of the centers were tertiary referral centers with or without attached maternity hospitals. Therefore, the proportion of genetic, structural, and metabolic etiologies may be somewhat higher than encountered in other neonatal units.

We used an informal Delphi-like process (up to 2 discussion rounds) with 3–9 reviewers. If no agreement could be achieved, the seizure would be assigned as unclassified. Videos of all cases were reviewed by members of the task force who were blind to etiology. The semiology of the events was evaluated, and each seizure was classified based on the proposed classification. Definitions and descriptions of the different seizure types were agreed using ILAE definitions.[4–7] The predominant seizure types were defined as (a) automatism, (b) focal clonic, (c) epileptic spasms, (d) myoclonic, (e) focal tonic, (f) autonomic, (g) behavioral arrest, (h) sequential, (i) unclassified, and (j) electrographic only.

An electrographic seizure was defined as an electrographic event with a pattern characterized by sudden, repetitive, evolving stereotyped waveforms with a beginning as well as an end which may or may not be accompanied by paroxysmal clinical changes. No minimum duration

was specified as long as there was sufficient demonstration of evolution in frequency and morphology of the discharge. The exceptions to the concept of evolving waveforms were electroclinical seizures, such as myoclonic seizures and epileptic spasms, which were associated with an EEG correlate that is very brief and not evolving. EEG was used to confirm that an event was an epileptic seizure, but not further analyzed. Polygraph channels included electrocardiogram (ECG), surface electromyography (EMG), respiration, and oxygen saturation in addition to blood pressure. However, the latter channels apart from ECG were not available in all EEG recordings.

3.1 | Statistical analysis

An overall association between seizure type and etiology was examined with a chi-squared test. The rate of each etiology category was estimated by seizure types, in other words, how much likely a baby with a certain seizure type has the specific cause. Its 95% confidence interval (CI) was calculated simultaneously, assuming a multinomial distribution for etiology categories.[8] Then, a forest plot was used to compare the rate of specific etiology between seizure types and further tested using a Fisher's exact test.

4 | RESULTS OF THE EVALUATION OF THE PROPOSAL

A total of 157 events from 146 neonates were reviewed by members of the ILAE Task Force on Neonatal Seizures. Ten infants were excluded because of (a) poor video quality ($n=7$) or (b) the EEG did not conclusively confirm a seizure ($n=3$). The remaining events consisted of 147 seizures in 135 neonates (12 infants had two different seizure types each). Demographics are summarized in Table 1. The most common etiology was HIE in term infants (25%) and intraventricular hemorrhage in preterm infants (45%). Preterm is defined as infants born before 37 weeks of pregnancy are completed. The neonatal period in the term infant is the first 28 days of life. In the preterm infant, this period extends to 44 completed weeks of gestational age. We were able to classify all seizures according to the ILAE neonatal classification framework, with no "unclassified seizure." Figure 1 details the etiologies of the seizure types, and Figure 2 describes the likelihood that the semiology is associated with the specific etiology. The most common seizure type was electrographic-only, in term (45/131 seizures) and in preterm infants (14/20 seizures). Notably, etiologies causing provoked seizures (HIE, vascular, infections, and preterm brain injury) were associated with electrographic seizures, while etiologies causing neonatal epilepsy (genetic causes, inborn error of metabolism, and cortical malformations) had electrographic seizures less commonly. We observed that the rate of HIE etiology of the babies with electrographic seizures was significantly higher than the HIE etiology rate of babies with sequential ($p=.006$) and myoclonic seizures ($p=.024$). Table 2 shows the detailed information of each etiology probability per seizure type. Unilateral clonic seizures were typically seen in association with vascular etiologies (term infants only). The babies with clonic seizures had a significantly higher rate of vascular etiology than the vascular etiology rate of babies with electrographic ($p=.008$), sequential ($p<.001$), and tonic seizures ($p=.005$). The term vascular etiologies included neonatal arterial ischemic stroke, intraventricular hemorrhage, and intraparenchymal hemorrhage. Most infants with intraventricular hemorrhage had electrographic-only seizures (6/9); other seizure types included myoclonic, autonomic, and tonic seizures. The majority of the infants with acute ischemic stroke had unilateral clonic seizures (11/19); other seizure types observed were electrographic-only seizures (6/19) and autonomic seizures (2/19). The majority of preterm infants exhibited only electrographic-only seizures regardless of etiology (13/19).

TABLE 1 Demographics of 135 neonates included in the data collection.

	Term	Preterm
Total	116	19
Sex		
Male	61	10
Female	55	9
GA mean (wks)	39.2	29
GA range (wks)		
PMA at EEG (wks)	40.2	31
PMA range (wks)		
Etiology		
HIE	29	5
Structural		
Vascular	22*	9**
Cortical malformation	6	1
Genetic	25	
Infections	11	4
Metabolic		
Inborn errors of metabolism	15	
Acute metabolic	3	
Unknown	6	

Abbreviations: EEG, electroencephalography; HIE, hypoxic–ischemic encephalopathy; PMA, postmenstrual age; wks, weeks.

*Acute ischemic stroke: $n=19$, intraventricular hemorrhage: $n=1$ and intraparenchymal hemorrhage: $n=2$. **Intraventricular hemorrhage: $n=8$ and intraparenchymal hemorrhage $n=1$.

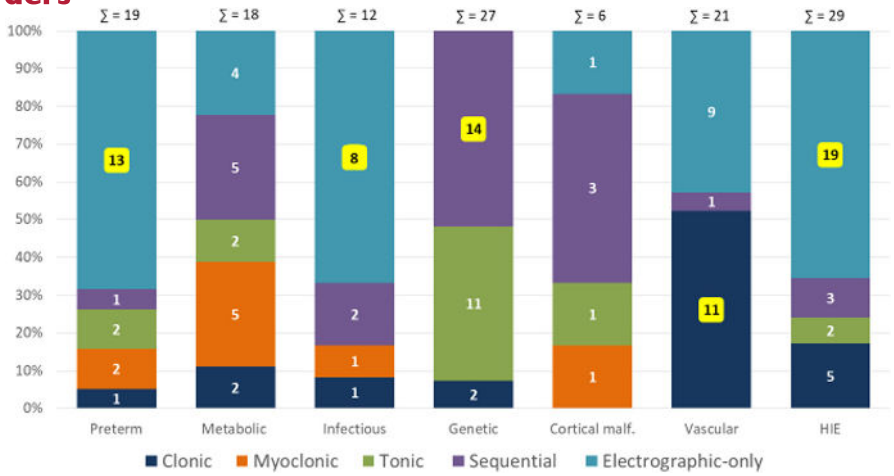

FIGURE 1 Etiologies/Groups of common seizure types in 146 neonates. Electrographic-only seizures were the most common seizure type in HIE, vascular, infectious, and preterm brain injury while clonic seizures were the most common seizure type in vascular causes and sequential seizures in genetic causes. Myoclonic seizures were seen in metabolic cases and no typical seizure type was seen in seizures due to cortical malformations. Infrequent seizure types (automatisms, autonomic seizure, behavioral arrest, and epileptic spasms) were seen in <5 neonates, respectively, and are not included in this graph.

TABLE 2 The rate of etiology (95% CI) by seizure semiology. The most likely etiologies by the seizure type were denoted in bold-faced font, to cover the higher percentages of causes.

	Electrographic	Sequential	Clonic	Tonic	Myoclonic
HIE	**38.6% (26.3–52.5)%**	10.3% (0–30.3)%	26.1% (8.7–47.9)%	15.8% (0–39)%	0% (0–36.3)%
Vascular	**28.1% (15.8–42)%**	3.4% (0–23.4)%	**47.8% (30.4–69.6)%**	5.3% (0–28.5)%	22.2% (0–58.5)%
Genetic	1.8% (0–15.6)%	**51.7% (37.9–71.7)%**	4.3% (0–26.1)%	**63.2% (47.4–86.3)%**	0% (0–36.3)%
Metabolic	7% (0–20.9)%	17.2% (3.4–37.2)%	8.7% (0–30.5)%	10.5% (0–33.7)%	**55.6% (33.3–91.8)%**
Infectious	17.5% (5.3–31.4)%	6.9% (0–26.9)%	4.3% (0–26.1)%	0% (0–23.2)%	11.1% (0–47.4)%
Cortical malformation	3.5% (0–17.4)%	10.3% (0–30.3)%	0% (0–21.8)%	5.3% (0–28.5)%	11.1% (0–47.4)%
Unknown	3.5% (0–17.4)%	0% (0–20)%	8.7% (0–30.5)%	0% (0–23.2)%	0% (0–36.3)%

Tonic seizures and sequential seizures were most commonly observed with genetic etiologies, showing significantly higher rates than those of other major seizure types (electrographic, clonic, myoclonic, all $p < .05$). Myoclonic seizures were seen in infants with inborn errors of metabolism, and their rate is higher than the metabolic etiology rate of babies with electrographic, sequential, clonic, and tonic, respectively (all $p < .05$).

Epileptic spasms and autonomic seizures were uncommon seizure types, while automatisms and behavioral arrest were very rare to be the dominant seizure manifestation in our group of patients. The latter two were only seen in one patient. Both types were more often seen as part of a sequential seizure. Due to low numbers, possible correlation to a specific etiology could not be determined.

5 | DISCUSSION

The ILAE neonatal classification[3] uses terminology consistent with the 2017 ILAE Classification of Seizures and the Epilepsies[5] while taking into account the specificities of seizures occurring in the neonatal period based on their electroclinical phenotype. The classification enables clinicians to identify neonatal seizures using a

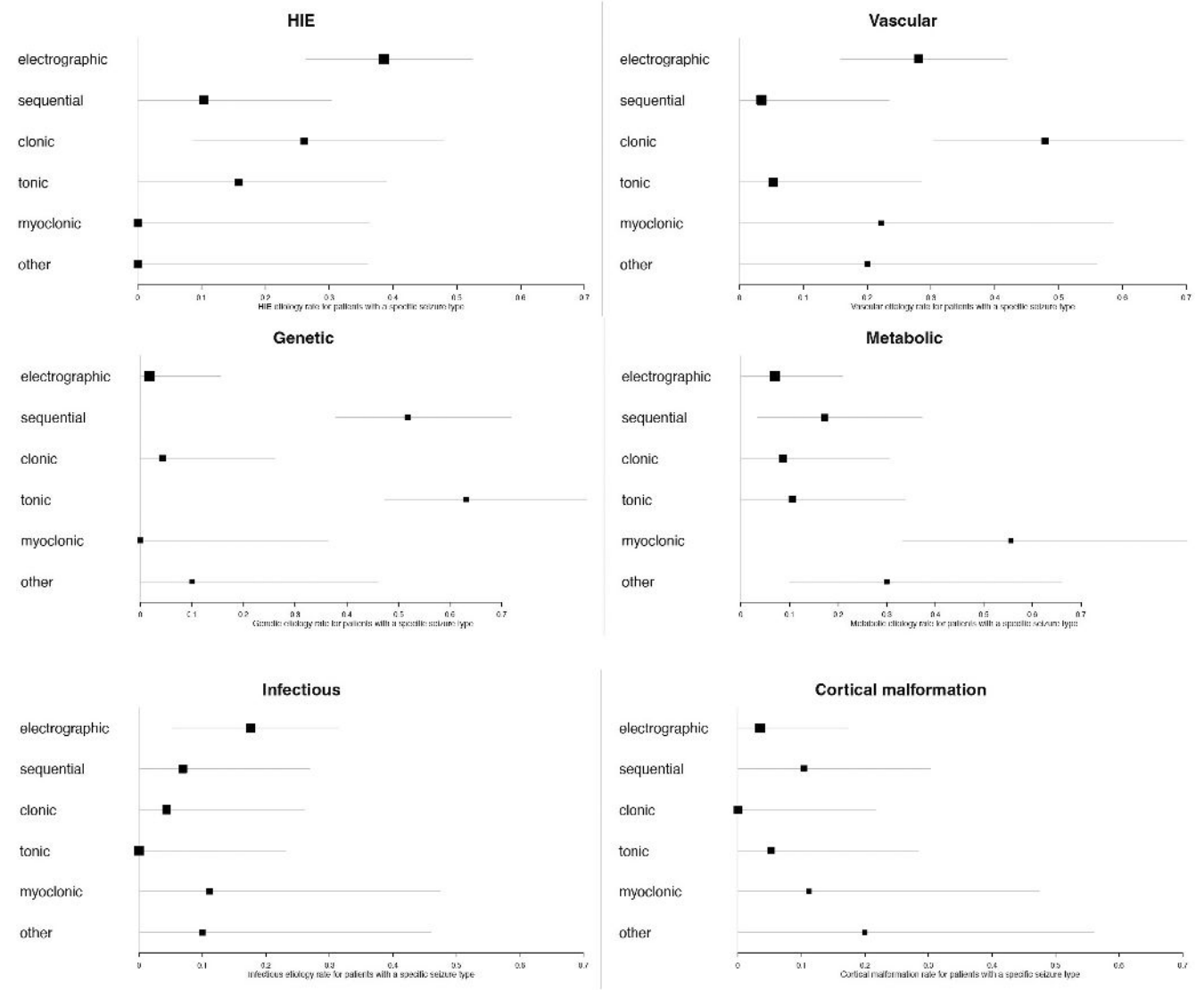

FIGURE 2 A forest plot to compare the specific etiology rate between seizure types. A square represents the estimated proportion, and a line indicates its 95% confidence interval. The size of square was determined by the precision of the estimated rate.

common language. The predominant seizure type is useful in directing the clinician in the appropriate path regarding etiology for a rapid diagnosis and treatment plan.

Through the use of the neonatal ILAE classification framework and reliably determining predominant seizure type, neonatologists and neurologists can obtain an improved perspective on etiology. This study demonstrated that clonic seizures were often due to a vascular etiology, tonic and sequential seizures were due to a genetic etiology, myoclonic seizures were often due to a metabolic etiology, and electrographic seizures were often due to HIE or vascular etiologies. Our results provide a clear direction regarding seizure semiology and etiology. In a systematic review by Nunes et al.,[2] certain seizure types were also deemed more indicative of specific etiologies. Similar to our study, clonic seizures were usually associated with a vascular etiology.[2] Similar findings were also noted by Dilena et al.[9] Sequential seizures and tonic seizures, characterized by asymmetric tonic posturing, more commonly were observed in neonates with a pathogenic variant. This has important clinical significance depending on the specific pathogenic variant. For instance, sodium channel-blocking agents can be given early if a channelopathy is suspected.[10–12] When sequential seizures occurred, focal tonic seizures were often part of sequential seizures regardless of etiology. They were etiologically associated with a range of conditions that included metabolic, vascular, HIE, and cortical malformations as well as undetermined conditions. A myoclonic component in sequential seizures often was seen in metabolic etiologies. Our study found a similar association between seizure type and etiology as a previous systematic review.[2]

A prospective multicenter cohort study by Mehta et al. found that 85.2% (23 or 27 neonates) of neonates with

infectious etiology had electrographic-only seizures. Mehta et al. identified that acute intracranial infection was the cause of seizure in 9% of neonates and that high seizure burden was associated with a worse neurodevelopmental outcome in these neonates.[13] It is important to monitor such neonates electrographically since our data also demonstrate that electrographic seizure burden is high in an infectious etiology. Our findings are in agreement with a recent retrospective study by Cornet et al. demonstrating that neonates with genetic etiologies were found to have either tonic or myoclonic seizures.[12] They found that in neonates with acute provoked seizures due to HIE, 42% had electrographic only and the majority of the remainder had clonic seizures. A third study reporting similar results was Santarone et al. who demonstrated that focal clonic seizures were associated with stroke and infectious etiologies.[14] de Corrêa's results differed slightly, but their cohort was based on a small sample size and lack of ictal EEG recordings in all patients. They did not identify any significant correlation between seizure etiology and semiology, perhaps because HIE was the most prevalent etiology (46.4%) and the other etiological categories were numerically underrepresented.[15] Although further large-scale prospective studies to truly establish this relationship, these preliminary relationships identified can direct caregivers in the initial workup.

Although neurophysiological monitoring is ideal in the initial assessment, it is not available worldwide or around the clock. However, some semiologies are more likely to be seizures than others. Pellegrin et al.[16] described case definitions of seizures that may be applied at the bedside, based on "Levels of Diagnostic Certainty," when EEG is not available. They proposed that (a) a clinical event with an EEG correlation gives you level 1 degree of diagnostic certainty as a "definite seizure"[16] and (b) focal clonic or focal tonic seizures directly witnessed, or reviewed on videotape, by experienced medical personal can be considered "probable seizures" and diagnosed even in the absence of EEG confirmation (level 2). Based on this, focal clonic or focal tonic seizures are more likely to be diagnosed accurately without an EEG and may be considered a "probable seizure." Therefore, when a focal clonic seizure is seen at the bedside, the clinician should evaluate for stroke since this seizure type is mostly associated with that etiology.

Our study has limitations. One limitation of this study is that the video-EEG samples were selected from several international tertiary centers. The numbers were small, and the seizures were not a consecutive sample of seizures or representative of a population. This may have created a bias in the sample since they may not have all been typical cases or reflective of a population. The authors of this study were blind to the patient's history other than the etiology; in particular, it was not known whether the neonate had received antiseizure medication (ASM) prior to the EEG. This may have influenced the number of patients with electrographic-only seizures and whether they were secondary to electroclinical dissociation induced by a given ASM. Because of hospital protocols, neonates with HIE or IVH are more likely to receive video EEG monitoring to screen for seizures, so this may have contributed to higher electrographic seizures. A potential conflict of interest is that the authors of this study were also members of the Task Force on neonatal seizures and were involved in the creation of the new ILAE neonatal seizure classification. Additional prospective studies with large cohorts of neonates from multiple countries are needed to further evaluate these associations.

6 | CONCLUSION

This study demonstrated that the ILAE neonatal classification can be used to aid in identifying the etiology of the neonatal seizure. Most neonatal seizures are reactive events with acute and possibly treatable etiologies. Neonatal epilepsies are now defined, often with known pathogenic variants. Suspecting a genetic etiology earlier can help facilitate prognostic and treatment recommendations. Knowing the trends between common clinical semiology and associated etiology can aid in the evaluation and treatment process. The faster the etiology can be determined, the quicker it can be appropriately treated.

AUTHOR CONTRIBUTIONS

E.G.Y. wrote the manuscript. J.Y.M. conducted all statistical analyses. All authors reviewed the drafts and final manuscript.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Test yourself

1. Clonic seizures are most indicative of what etiology?
   A. Infection
   B. HIE
   C. Stroke
   D. Genetic
   E. Metabolic
2. Tonic seizures are most indicative of what etiology?
   A. Infection
   B. HIE
   C. Stroke
   D. Genetic
   E. Metabolic
3. Myoclonic seizures are most indicative of what etiology?
   A. Infection
   B. HIE
   C. Stroke
   D. Genetic
   E. Metabolic

Answes may be found in Data S1.