The ILAE Classification of Seizures & the Epilepsies: Modification for Seizures in the Neonate. Proposal from the ILAE Task Force on Neonatal Seizures

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Abstract

Seizures are the most common neurological emergency in the neonatal period occurring in 1–5 per 1000 live births. In contrast to seizures in infancy and childhood, most seizures in the neonate are symptomatic of an acute illness and can be electrographic only or associated with clinical manifestations. Hence, neonatal seizures may not fit easily into classification schemes for seizures and epilepsies primarily developed for older children and adults. The Task Force on Neonatal Seizures was established with the aim of developing a modification of the 2017 ILAE Classification of Seizures and Epilepsies, relevant to neonates. The proposed neonatal classification framework emphasizes the role of EEG in the diagnosis of seizures in the neonate and includes a classification of seizure types relevant to this age group. The seizure type is typically determined by the predominant clinical feature. As seizures in neonates are often electrographic only with no clinical feature, these are included in the proposed classification. Clinical events without an EEG correlate are not included. As seizures in the neonatal period have been shown to have a focal onset, a division into focal and generalized is unnecessary. Seizures can have a motor (automatisms, clonic, epileptic spasms, myoclonic, sequential, tonic) or non-motor (autonomic, behavior arrest) presentation. The proposed classification allows the user to choose the degree of detail when classifying seizures in this age group.

The proposed classification was successfully applied to 147 video-EEG recordings of neonatal seizures. These included representative samples of the common etiologies; hypoxic ischemic encephalopathy, stroke, infection, metabolic and genetic disorders. We noted that certain seizure types were associated with particular etiologies emphasizing the value in describing seizure types in this age group.

Keywords: Neonatal seizures, EEG, semiology, classification, epilepsy

Key points:

- A new framework is proposed for seizures in neonates, in keeping with 2017 ILAE seizure classification while tailored to the neonatal period
- The framework emphasizes the necessity of EEG diagnosis of seizures in the neonatal period.
- Seizures can occur with clinical manifestations (motor or non-motor) or without clinical manifestations (electrographic only).
- Descriptors are determined by the predominant clinical feature and divided into motor and non-motor.

Definitions

For the purpose of this report, the following definitions are used: [1,2]

- Gestational age (GA): time elapsed between the first day of the last menstrual period and the day of deliver (completed weeks).
- Postmenstrual age (PMA): gestational age plus chronological age (in weeks).
- Conceptional age (CA): age from conception: PMA minus 2 weeks.
- Preterm infant: born before GA of 37 weeks.
- Neonatal period: Period from birth up to and under 28 days in term neonates, or from birth up to a PMA of 40 weeks and under 28 days in preterm neonates.

Introduction

The 2017 ILAE Position Papers on Classification of Seizure Types and the Epilepsies[3,4] presented a framework for classification including seizure types, epilepsy types, and syndromes. There is an emphasis on defining etiology at all levels of clinical classification in addition to consideration of comorbidities. Terminology is updated with some new seizure types included. The ILAE Commission on Classification & Terminology recognized that seizures in the neonate require special considerations and therefore a Neonatal Task Force was established with the aim of integrating seizures and epilepsies in this age group into the 2017 ILAE Classification.

Seizures are the most common neurological emergency in the neonatal period occurring in 1–5 per 1000 live births. The majority of neonatal seizures are symptomatic of an acute illness with an underlying etiology either documented or suspected.[5,6] Epilepsy syndromes may present in the neonatal period and with the increasing availability of genetic testing expanding numbers of neonatal epilepsies with genetic and metabolic etiologies are recognized.[7] Although many causes can give rise to neonatal seizures, a relatively small number account for most seizures (Figure 1).

The clinical diagnosis of neonatal seizures is difficult, particularly in critically ill infants due to the multitude of epileptic and non-epileptic clinical manifestations within the intensive care setting.[12,13] In the study by Malone,[14] 20 video clips of paroxysmal events in neonates were presented to 137 health professionals (mostly neonatologists and intensivists) with the aim of classifying movements as seizure or non-seizure. Only 50% of events were correctly classified. There was poor inter-observer agreement independent of observers' specialty. The immature state of the motor pathways[15,16] in term and preterm neonates may account for some of the difficulty in differentiating seizures from non-epileptic movements.[17] In

selected populations, particularly in infants with hypoxic-ischemic encephalopathy (HIE), 50-80% of seizures are electrographic only and, as a result, the extent of the seizure burden (time spent with seizures; defined as electrographic seizures in minutes per hour) may be greatly underestimated. [6,12-14,18] It has been suggested that hypothermia therapy for HIE may also increase electro-clinical uncoupling of seizures, with a high incidence of electrographic seizures in these infants.[12] There is evidence that electrographic seizure burden has a comparable effect on outcome as electro-clinical seizures.[19-23]

The ILAE defines a seizure as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain; [3,24] however, a seizure does not necessarily mean that a person has epilepsy. Electrographic only seizures are not included in this definition.

Neonatal seizures are often categorized as clinical only, electro-clinical, or electrographic-only.[13,25] A clinical only seizure consists of a sudden paroxysm of abnormal clinical changes without a definite EEG association. Whether or not all of these events are indeed of epileptic origin remains uncertain in newborns. An electro-clinical seizure features definite clinical signs simultaneously coupled with an electrographic seizure. An electrographic only seizure refers to the presence of a definite EEG seizure that is not associated with any evident clinical signs (synonyms: clinically silent or subclinical seizures). The term electrographic only is preferred as this depends on observational methods used and the seizure may not be truly subclinical.

The American Clinical Neurophysiology Society has recently defined an electrographic neonatal seizures as a paroxysmal abnormal, sustained change in the EEG, characterized by a repetitive and evolving pattern with a minimum 2 μV voltage (peak to peak) and duration of at least 10 seconds.[26] This definition does not require any evident clinical change.

However, this definition has been challenged as brief runs of rhythmic discharges (BRD) or brief rhythmic ictal discharges (BIRDs) were shown to be associated, like electrographic seizures, with clinical manifestations and poor outcome. [27,28]

Historical review

Historical efforts to characterize and classify neonatal seizures have been directed towards emphasizing how they differ from those of older children and adults. In this report our aim is to use terminology consistent with the 2017 ILAE Classification of Seizures and the Epilepsies. [3,4,24]

Studies in the 1950's and early 1960's focused on motor and behavioral changes and were based upon direct observation with or without EEG recordings. [29-31] This resulted in the use of terms such us focal clonic and generalized tonic for neonatal seizure classification (generalized tonic-clonic seizures were considered non-existent in this age group). Eventually, myoclonus was added to the growing classification.[32]

Early investigators recognized autonomic nervous system changes including variation in respiratory rate, vasomotor changes, salivation, heart rate and blood pressure as seizure manifestations. Polymorphic and atypical clinical events were described, the latter including staring, sudden awakening and alerting, eye deviation, eye blinking, nystagmus, chewing and limb movements resembling "swimming, rowing, and pedaling".[33] These descriptions were incorporated into classifications schemes as a category of "anarchic",[31] "minimal" [34] or "subtle"[35]. These findings resulted in the classification proposed by Volpe which included: multifocal clonic, focal clonic, tonic, myoclonic and subtle seizures.[35,36]

Using EEG-video analysis of electro-clinical correlations,[37] it was recognized that some clinical events previously reported as seizures were in fact non-epileptic. Indeed, many of these clinical events were found to occur without EEG correlate and could be provoked by stimulation and suppressed by restraint.[13] This led to a reconsideration of the classification of neonatal seizures based upon either pathophysiology (epileptic versus non-epileptic); electro-clinical relationships (electro-clinical, clinical only, electrical only); or behavioral (focal clonic, focal tonic, myoclonic, spasms, generalized tonic, motor automatisms – each with additional modifiers to suggest whether they were considered to be of epileptic or non-epileptic origin). The term motor automatisms included: ocular movements, oral-buccal-lingual movement, and progression movements of the limbs (pedaling, swimming, rowing). The basic movements and behaviors of earlier classification systems were preserved and epileptic spasms were added. In addition, a significant group of neonatal seizures were considered to have only an electrographic signature with no clinical correlate.[13]

With the advent of prolonged bedside electrographic monitoring in the Neonatal Intensive Care Unit (NICU), either with EEG or with amplitude integrated EEG (aEEG), it has been increasingly recognized that electrographic seizures without clinical correlates are frequent, particularly in critically-ill neonates.[18,38,39] As a result, the definition of neonatal seizures has been reconsidered, now with a focus on the electrographic basis of the events, either with or without clinical manifestations. [40]

Proposal

The goal of this report is to propose a classification of seizures in neonates that can fulfil the following criteria:

- Integrate into the 2017 ILAE Classification
- Be based on electro-clinical phenotype
- Emphasize the key role of EEG in the diagnosis of neonatal seizures
- Have implication for management and treatment of events
- Be acceptable to neonatologists, pediatricians, epileptologists, neurophysiologists, and neurologists.
- Be applicable in all health care settings.

Figure 2 depicts the proposed approach for seizure classification.

Presentation

Newborns may present with paroxysmal clinical events suspected to be epileptic seizures; these include motor or non-motor phenomena.

Diagnosis

In neonates, video-EEG recording is the gold standard for diagnosis. [13,41-43] A proportion of seizures are electrographic only, particularly in encephalopathic and critically ill patients. [12,18,38,44] In the neonate, this may occur because of the immaturity of the central nervous system. Uncoupling may increase after administration of antiseizure medications, particularly phenobarbital. [13,18,39,45-47] Therefore, electrographic-only seizures should to be part of the classification. The initial stage of description of a neonatal seizure should specify

whether a seizure is with (electro-clinical) or without clinical signs (electrographic only). Electro-clinical dissociation is the phenomenon when a clinical seizure type occurs at times with and at times without an associated rhythmic EEG discharge in a given patient.[45,46] However this is considered to be a rare occurrence and by definition implies that electrographic seizures (with or without clinical correlate) also occur in that given patent. Therefore, only events with EEG correlate are included in this proposal.

Seizure types

We used the definition of seizure type as suggested by Fisher and colleague,[3] a useful grouping of seizure characteristics for purposes of communication in clinical care, teaching, and research.

The basic principles of the 2017 ILAE classification of seizure types[3] (see appendix Figure A) are based on the 1981 classification with the initial division of seizures into those of focal and generalized onset.[48,49] As newborns have been shown to have seizures with exclusively focal onset, [13,50] the initial division into focal and generalized is unnecessary. The second step in the 2017 ILAE classification is the division into aware and unaware (impaired awareness) seizures, however, this is not applicable to neonates as it is not possible to confidently and reproducibly assess awareness and responsiveness in this age group. This is followed by the division into motor and non-motor seizures and finally by the seizure type (Table 1). In the 2017 ILAE classification, focal seizures are determined by the first feature, as seizure localization has important clinical implications to identify a possible focal lesion irrespective of etiology. While seizures in neonates can present with a variety of clinical signs, in the majority of cases a single *predominant* feature can be determined. Pragmatically, it appears best to classify seizures according to the predominant clinical

manifestation, as this is more likely to have clinical implications for etiology than determination of the seizure onset zone. This may or may not be the first clinical manifestation. For example, a neonate may present with a focal tonic posturing and in addition have some ocular myoclonus – this can still be classified as a tonic seizure.

In some situations, it may be difficult to identify the dominant feature, typically in longer seizures where a sequence of clinical features can be seen, often with changing lateralization. Events with a sequence of signs, symptoms, and EEG changes at different times have been described as a sequential seizure in the 2017 ILAE classification manual[51]. As this is often seen in neonates this term was added to the seizure types.

Several seizure types described in the 2017 ILAE classification[3,51] cannot be diagnosed in newborns due to lack of verbal and limited non-verbal communications. These include sensory seizures, cognitive and emotional seizures. Sensory seizures are defined as a perceptual experience not caused by appropriate stimuli in the external world. Such seizures can in rare cases produce reproducible semiology but it is assumed that in the majority of cases they would appear as electrographic only events. Awareness and responsiveness cannot be accurately assessed in neonates and hence not readily classified; however, this may change with more advanced technology or detailed observation. Similarly, somatosensory or visual auras cannot be determined in neonates. Due to the relative low muscle tone and supine position of newborns, the occurrence of atonic seizures cannot be evaluated clinically without invasive methods. These seizure types are therefore not included in the proposed framework. Motor seizures can be further described using modifiers listed in Table 2.The framework allows the user to classify the seizure in as much detail as required in a certain situation. The full description would include manifestation, a descriptor and etiological diagnosis.

Epilepsy syndromes

While the majority of seizures in the neonatal period occur in the context of an acute illness, in some cases the seizures may be the first manifestation of early-onset epilepsy. Early differentiation of acute symptomatic seizures from neonatal-onset epilepsies has important therapeutic and prognostic implications since the evaluation and long-term management of neonatal epilepsies are distinct from those of acute symptomatic seizures.[7] Syndromes presenting in the neonatal period include: self-limited (benign) familial neonatal epilepsy, early myoclonic encephalopathy (EME), and early infantile epileptic encephalopathy (Ohtahara syndrome).[70]

Recent advances in neuroimaging and genomic technology as well as the implementation of video-EEG in the NICU, allow for the identification of more discrete, etiology-specific neonatal epilepsy syndromes than previously recognized.[71] It is likely that the combination of more sophisticated genetic testing and video-EEG monitoring will allow the identification and stratification of distinct etiology-specific electro-clinical phenotypes,[72] as suggested in the new ILAE classification of the epilepsies (Figure 3).[4]

Evaluation of the proposal

Methods

During a 2-day workshop and face-to-face meetings the classification and framework were tested by reviewing of video-EEG data of neonatal seizures. Inclusion criteria for the data collection were as follows: (1) Consecutive and unselected cases from neonatal units at Albert Einstein College of Medicine, Baylor College of Medicine, Helsinki University Central Hospital, PUCRS School of Medicine, Royal Hospital for Children Glasgow, UCL-Institute of

Child Health, and University of California San Francisco, and (2) Adequate EEG and video quality to verify ictal event and to review semiology. In order to represent common etiologies, we decided to include a minimum of 30 cases with HIE, 20 with stroke or hemorrhages, 20 with infectious causes, 20 with inborn errors of metabolism, 20 with genetic causes, and 10 with cortical malformations.

A selection bias is recognized as most of the centers are tertiary referral centers with or without attached maternity hospitals. The proportion of genetic, structural and metabolic etiologies may be somewhat higher than seen in other neonatal units.

The videos of all cases were reviewed by the members of the task force, the semiology evaluated and the seizure classified based on the proposed classification.

An electrographic seizure was defined as an electrographic event with a pattern characterized by sudden, repetitive, evolving stereotyped waveforms of with a beginning and 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 are clinical seizures such as myoclonic seizures and spasms which are associated with an EEG correlate that is very brief and not evolving. The EEG was used to confirm that an event was an epileptic seizure but not further analyzed.

Results

A total of 157 events from 146 neonates were reviewed. Ten infants were excluded because of poor video quality (n=7) or EEG did not conclusively confirm a seizure (n=3), leaving a total of 147 seizures in 136 neonates. Demographics are summarized in Table 3. The most

common etiology was HIE in term infants (25%) and vascular (stroke or hemorrhage) in preterm infants (45%).

We were able to classify all seizures according to the proposed classification. Table 4 details the seizure type according to etiology. The most common seizure type was electrographic only both in term (45/131 seizures) and preterm infants (14/20 seizures). The most common etiologies of electrographic seizures were HIE and infection. Clonic seizures were typically seen in association with vascular etiologies (term infants only). Tonic seizures and sequential seizures were most commonly observed in genetic etiologies and myoclonic seizures in inborn errors of metabolism. All seizures in neonates with a genetic etiology had motor manifestations. Automatisms and behavioral arrest were uncommon as dominant seizure manifestation. In preterm infants 70% (14/20) of seizures were electrographic regardless of etiology. No dominant seizure type was seen for acute metabolic disorders, cortical malformations and unknown causes but numbers were too small for comparison.

Discussion

Seizure semiology is the description of signs and symptoms associated with an ictal event and is valuable in localizing the epileptogenic zone. However, in the neonate, the development within the limbic system with its connections to midbrain and brainstem is more advanced than the cerebral cortical organization,[73] leading to a higher frequency of oral automatisms, ocular changes such as eye deviation, apnea and clinical features related to the autonomic nervous system in neonates than in older children.

The neonatal classification proposed emphasizes the role of EEG in the diagnosis of seizures in the neonate and includes a classification of seizure types relevant to this age group. The

seizure type is typically determined by the predominant clinical feature while in the 2017 ILAE classification of seizures in other age groups, the seizure type was defined by the first manifestation. This was based on the assumption that the first manifestation may indicate whether the seizure may have a focal onset. Since all seizures in the neonate are focal, we propose to emphasize the predominant feature as this may provide clues regarding the etiology.

This concept was evaluated by the Task Force by reviewing 147 neonatal seizures. We demonstrated that the classification can be implemented in clinical practice. Among the seizures reviewed we noted that certain etiologies are associated with certain seizure types: most neonates with genetic etiologies have tonic seizures and / or sequential seizure, whereas in preterm infants (regardless of etiology) and neonates with HIE or infectious causes present most commonly with electrographic only seizures. Term infants with stroke are more likely to have focal clonic seizures. Myoclonic seizures are associated with inborn errors of metabolism.

Increased movements were noticed at arousal but we were not able to differentiate these from other arousals either on clinical grounds or by EEG. However, hyperkinetic phases were observed as part of sequential seizures. It was concluded that hyperkinetic events if occurring in isolation cannot be defined as seizures, but they may occur in the context of a sequential seizures.

Review of the literature and our own data suggest that seizure semiology in neonates may have diagnostic value in respect to etiology of seizures and /or outcome (see Table 5). However, many of these clinical associations are based on small case studies or with very limited description of semiology and will need to be tested on a larger dataset.

Clancy and Legido described electrographic only seizures in newborns as sudden, repetitive, evolving stereotyped waveforms with a definite beginning, middle, and end and a minimum duration of 10 seconds.[38] However, the choice of 10 seconds duration was explicitly arbitrary. Similarly an arbitrary minimum duration of 10 seconds is also applied to the definition of a seizure in critical ill adults.[87] This is in contrast to some electro-clinical seizures such as myoclonic seizures or spasms which are by definition shorter than 10 seconds.[3,51,88] Both in neonates and critically ill adults it has been suggested that rhythmic discharges of less than 10 seconds duration (so called BIRDs: Brief Interictal Rhythmic Discharges) are associated with seizures in the same or subsequent EEG recording[27,28,89,90] and an increased risk of abnormal neurodevelopmental outcome.[27] BIRDs are defined as very brief (<10 seconds) runs of focal or generalized sharply contoured rhythmic activity, with or without evolution, that are not consistent with any known normal or benign pattern, which in adults have a frequency greater than 4 Hz.[91] It is of interest that in these clinical studies BIRDs either showed no evolution[90,91] or the presence or absence of evolution has not been described.[27,28] It has been suggested that definite BIRDs with an evolution represent “very brief” electrographic seizures.[81]

We propose to define seizures in the neonatal period as an electrographic event with a pattern characterized by sudden, repetitive, evolving stereotyped waveforms with a beginning and end. However the duration has to be sufficient to demonstrate evolution in frequency and morphology of the discharges which will depend on the frequency of the discharge. The duration of this is to an extent arbitrary but need to be sufficient to allow recognition of onset, evolution and resolution of an abnormal discharge. BIRDs without evolution are not considered seizures but may serve as an early predictor of seizures during subsequent EEG monitoring and as a prognostic indicator. Notable exceptions are certain

clinical seizures such as myoclonic seizures and spasms which are associated with an EEG correlate that is very brief and not evolving. We acknowledge that with advanced technology this definition may change in the future.

In defining clinical and electrographic seizures, we acknowledge that treatment may alter both semiology and EEG features of these events, so that our definitions apply to seizure recorded prior antiepileptic drug therapy. Electrographic seizure burden and seizure frequency may impact the treatment approach, but the presence or absence of clinical signs should not.

It is recognized that clinical care for affected neonates is also provided in centers where resources and expertise are limited.[92] EEG is considered the gold standard for seizure diagnosis in the neonate, but in situations when and where it is not readily available, aEEG may be used,[93] although its limitations are well recognized.[94,95] If neither is available, we would like to refer to the algorithm for diagnosis and treatment of neonatal seizures in developing countries[92] which was developed as part of the Global Campaign against Epilepsy, an initiative by the ILAE and the World Health Organization (WHO). This document proposes pragmatic guidelines for the diagnosis and management of the most common and important conditions that may cause seizures in the neonatal period in centers with limited resources, where recommended diagnostic testing may not be possible. In such situations, clonic seizures may be identified more reliably than other seizure types[14] as well as focal tonic seizures and some sequential seizures whereas automatisms, autonomic seizures and seizures with behavioral arrest require EEG confirmation and electrographic seizures will, by definition, be missed without EEG. Beside maneuvers such as stimulation of the infant to provoke behaviors similar to spontaneously observed clinical event suspected of being seizures and restraint of infant limbs during spontaneous events to arrest the events can

help in identifying clinical events as exaggerated reflex behaviors and non-epileptic in origin.[13]

Although this framework was developed for seizures in the neonatal period, we believe that it can be readily applied to acute symptomatic seizures in critically ill patients of any age, particularly within the intensive care setting who may present with similar manifestations. Non convulsive seizures are common in critically ill patients[96] and electrographic only presentation due to electro-clinical uncoupling has been described in 2/3 of critically ill children with seizures.[97-99] However, the etiologies may vary with age.

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Figure legends

Figure 1: Common etiologies of neonatal seizures in term infants. Adapted from [5,6,8-11]

Figure 2: Proposed diagnostic framework of seizures in the neonatal period including classification of seizures. Adapted from 2017 ILAE seizure classification.[3] Neonates present with discrete events suspected to be epileptic seizures or are critically ill (often ventilated, sedated and treated with muscle relaxants in intensive care).

Figure 3: Framework for neonatal seizures. Adapted from 2017 ILAE Framework of the epilepsies.[4] For the purpose of this paper hypoxic events as separate entity because it is the most common etiology of seizures in this age group. There is no evidence at present that immune processes play a role in seizure etiology in this age group.

* Including perinatal hypoxic-ischemic encephalopathy and other hypoxic events in the neonatal period; ** Including infarction, hemorrhage, brain trauma and brain malformations.

Tables

Type	Description [3,51]	Special considerations for neonates
Automatisms	A more or less coordinated motor activity usually occurring when cognition is impaired. This often resembles a voluntary movement and may consist of an inappropriate continuation of preictal motor activity	Typically oral and usually in association with other features. Normal and abnormal behavior in term and preterm infants may mimic ictal automatisms. [13,52]
Clonic	Jerking, either symmetric or asymmetric, that is regularly repetitive and involves the same muscle groups	Seizure type best recognized clinically. [13,14,53,54]
Epileptic spasms	A sudden flexion, extension, or mixed extension–flexion of predominantly proximal and truncal muscles that is usually more sustained than a myoclonic movement but not as sustained as a tonic seizure. Limited forms may occur: Grimacing, head nodding, or subtle eye movements. May occur in clusters.	Rare. May be difficult to differentiate from myoclonic seizures without EMG channel. [55-57]
Myoclonic	A sudden, brief (<100 msec) involuntary single or multiple contraction(s) of muscles(s) or muscle groups of variable topography (axial, proximal limb, distal).	Clinically difficult to differentiate from non-epileptic myoclonus. [58-61]
Sequential seizure	This term is used in the instruction manual for the ILAE 2017 operational classification of seizure types for events with a sequence of signs, symptoms, and EEG changes at different times.[51]	No predominant feature can be determined, instead the seizure presents with a variety of clinical signs. Several features typically occur in a sequence, often with changing lateralization within or between seizures. [62-64]
Tonic	A sustained increase in muscle contraction lasting a few seconds to minutes.	Usually focal, unilateral or bilateral asymmetric. Generalized tonic posturing is often not of epileptic origin. [13,56,63,65]
Autonomic	A distinct alteration of autonomic nervous system function involving cardiovascular, pupillary, gastrointestinal, sudomotor, vasomotor, and thermoregulatory functions.	May involve respiration (apnea). Typically seen with other seizure manifestations. EEG confirmation mandatory. [13,66-70]
Behavioral arrest	Arrest (pause) of activities, freezing, immobilization, as in behavior arrest seizure.	May be focal and/or followed by apnea, other autonomic manifestations and motor seizures. [67]
Unclassified seizure type	Due to inadequate information or unusual clinical features with inability to place in other categories.	

Table 1: Integration with the 2017 ILAE Classification of Seizures and Epilepsies

Seizure type	Modifiers
Automatisms	Unilateral Bilateral asymmetric Bilateral symmetric
Clonic seizures	Focal Multifocal Bilateral
Epileptic spasms	Unilateral Bilateral asymmetric Bilateral symmetric
Myoclonic seizures	Focal Multifocal Bilateral asymmetric Bilateral symmetric
Sequential seizure type	Depending on components
Tonic seizures	Focal Bilateral asymmetric Bilateral symmetric

Table 2: Modifiers of motor seizures in the neonatal period

	Term	Preterm
Total	116	20
Gender		
Male	61	10
Female	56	9
GA mean (wks)	39.2	29
PMA at EEG (wks)	40.2	31
Etiology		
HIE	29	5
Structural		
Vascular	22	9
Cortical malformation	6	1
Genetic	25	
Metabolic		
Inborn errors of metabolism	15	
Acute metabolic	3	
Infectious	11	4
Unknown	6	

Table 3: Demographics of 136 neonates included in the data collection.

		Motor							Non-motor		
Diagnosis		**Auto-matisms**	**Clonic**	**Epileptic Spasms**	**Myoclonic**	**Sequential**	**Tonic**	**Autonomic**	**Behavioral arrest**	**Electro-graphic**	**total**
HIE	term		5			3	2			19	29
	preterm		1				1			3	5
Vascular	term		11			1		2		9	23
	preterm				2		1			7	10
Cortical malformation	term			1	1	3	1		1	1	8
	preterm									1	1
Genetic	term	1	2			14	11				28
	preterm										
IEM	term		1	3	5	4	2			3	18
	preterm										
Acute metabolic	term		1			1				1	3
	preterm										
Infectious	term		1		1	2				8	12
	preterm					1		1		2	4
Unknown	term		2					1		3	6
	preterm										
Total		1	24	4	9	29	18	4	1	57	147

Table 4: Seizure types according to etiology. HIE, infectious etiologies and seizures in premature infants were usually electrographic whereas the most common seizure type in genetic etiologies was sequential. Highlighted in yellow the most common seizures type for a given etiology. HIE: hypoxic ischemic encephalopathy, IEM: inborn errors of metabolism.

	Clinical context of seizure type	Current data review
Automatisms	Described as common seizure type in HIE and preterm infants. [13,52,53,74]	Very rare in isolation (<1%).
Clonic	Described as acute symptom of neonatal stroke or cerebral hemorrhage. [13,53,54,75-77]	Typical for vascular etiologies in term infants, also commonly seen in HIE.
Myoclonic	Typical seizure type in early myoclonic encephalopathy, but may be seen in other etiologies too, particularly in genetic epilepsy syndromes and preterm infants. Also seen in HIE and inborn errors of metabolism. [13,42,55,56,68,69,72,78]	Typical in inborn error of metabolism.
Sequential seizure	Often seen in channelopathies such as BFNE or KCNQ2 encephalopathy, but may be seen with other etiologies. [63,64,69,79]	Typical in genetic etiologies.
Spasms	Described in association with inborn error of metabolism or Ohtahara syndrome, here usually in form of tonic spasms (STXBP1, hemimegalencephaly). [42,56,58,60,61,78,80,]	Rare, mostly in inborn error of metabolism.
Tonic	Typical seizure type in early infantile epileptic encephalopathy (Ohtahara syndrome), but also seen in other epileptic encephalopathies and genetic neonatal epilepsies (eg KCNQ2 and KCNQ3 mutations). May be seen in HIE. [13,56,57,63,65,69,72,78,81]	Typical in genetic etiologies.
Autonomic	Described in intraventricular hemorrhage as well as temporal or occipital lobe lesions, typically as apnea and cyanosis. Also described in Ohtahara syndrome. [13,64,66,81-84]	Overall rare in isolation (<5%).
Behavioral arrest	Arrest (pause) of activities, freezing, immobilization.	Very rare in isolation (<1%).
Electrographic only seizures	Typical in preterm infants, HIE (particularly in those with basal ganglia/thalamus injury) and neonates undergoing cardiac surgery. [6,11-13,17,85,86]	Most common seizure type in preterm infants, HIE and infectious causes.

Table 5: Clinical relevance of seizure types in the neonatal period: review of literature and own data.

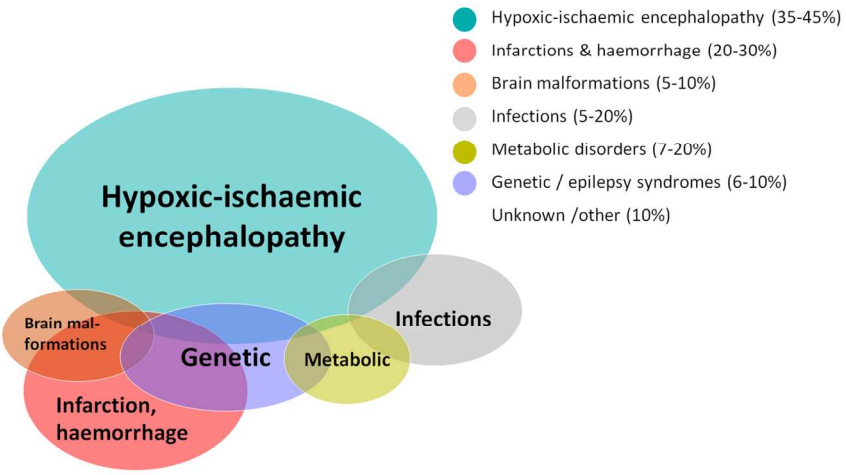

Figure 1: Common etiologies of neonatal seizures in term infants. Adapted from 5,6,8-11

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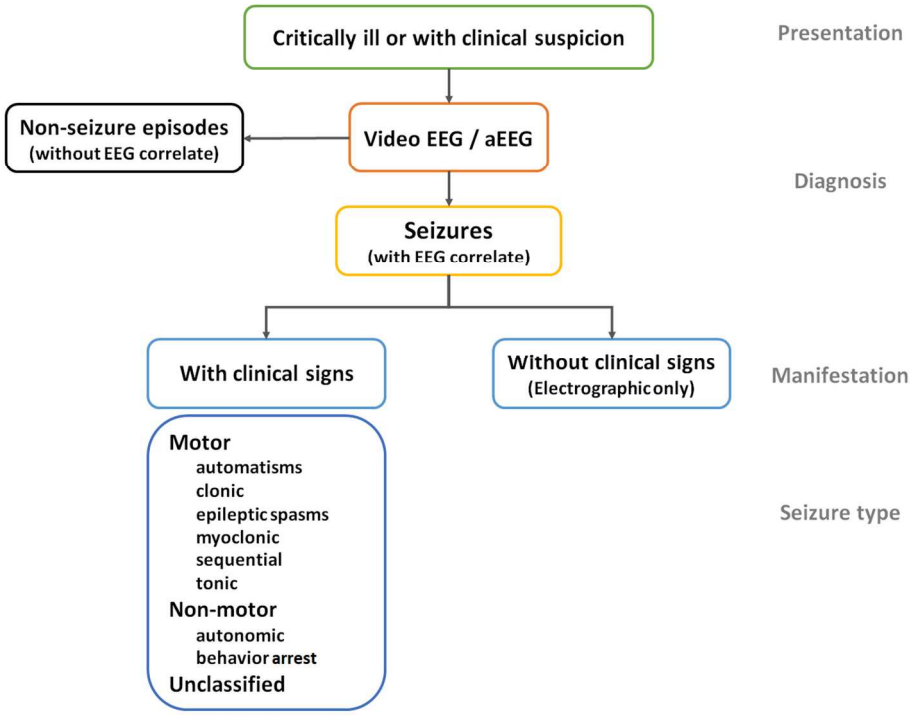

Figure 2: Proposed diagnostic framework of seizures in the neonatal period including classification of seizures. Adapted from 2017 ILAE seizure classification.3 Neonates present with discrete events suspected to be epileptic seizures or are critically ill (often ventilated, sedated and treated with muscle relaxants in intensive care).

90x69mm (600 x 600 DPI)

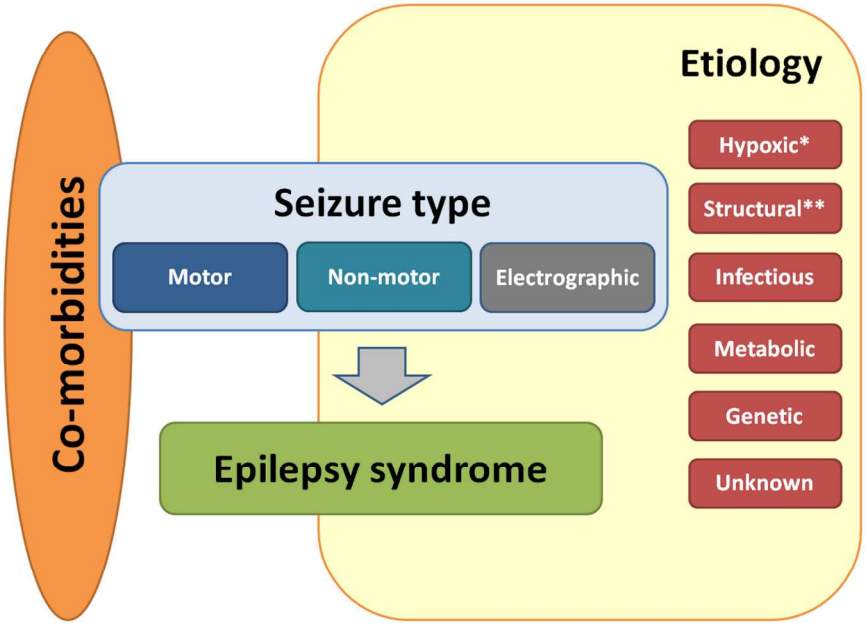

Figure 3: Framework for neonatal seizures. Adapted from 2017 ILAE Framework of the epilepsies.4 For the purpose of this paper hypoxic events as separate entity because it is the most common etiology of seizures in this age group. There is no evidence at present that immune processes play a role in seizure etiology in this age group.
* Including perinatal hypoxic-ischemic encephalopathy and other hypoxic events in the neonatal period; ** Including infarction, haemorrhage, brain trauma and brain malformations.

88x64mm (600 x 600 DPI)