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COMMENTARY

Neonatal seizures reach the mainstream: The ILAE classification of seizures in the neonate

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1 | INTRODUCTION

Neonatal seizures, with their distinct electroencephalographic (EEG) patterns and etiologies, have long been set apart from the seizures of older children and adults. Newborns were included in the 2010 International League Against Epilepsy (ILAE) terminology and concepts for organization of seizures and the epilepsies.[1] However, the 2017 ILAE operational classification of seizure types[2] specifically called for a separate task force to develop a classification of neonatal seizures because "seizures in the neonate can have … little or no behavioral manifestations." The new "ILAE Classification of Seizures and the Epilepsies: Modification for Seizures in the Neonate"[3] is a major advance for the field of neonatal neurology. A few controversial areas remain, however, and key points ought to be emphasized.

2 | THE CRITICAL IMPORTANCE OF EEG CONFIRMATION FOR NEONATAL SEIZURE DIAGNOSIS IS NOW UNDERSCORED BY ILAE

It should be no surprise that seizures that do not originate from, or migrate to, the motor cortex do not result in obvious movements. Because newborns are preverbal, they are not able to communicate sensory phenomena associated with seizures. Furthermore, clinical observation of neonates in an intensive care setting is often inhibited by isolette coverings, dark lighting, and other environmental features of modern neurocritical care. Even if an infant's seizures result in stereotyped movements, the most careful clinician may well miss them. Thus, the new classification of neonatal seizures encourages description of motor manifestations, but does not require a clinical correlate for an electrographic-only seizure diagnosis.

Another major improvement in the current classification is that paroxysmal clinical events must have an EEG signature to be diagnosed as seizures. Clinical episodes that have no ictal EEG correlate are not seizures. The ambiguous "EEG-negative seizure" concept is eliminated. This should improve diagnostic specificity and spare infants without seizures from treatment with unnecessary antiseizure medication.

The task force recognized that EEG monitoring is not universally available and offered the option to label seizures as "probable" or "possible." This may be unsatisfying to neonatal seizure researchers, but should be helpful to clinicians in lower resourced settings.

3 | A MAJOR CHANGE TO THE DEFINITION OF EEG SEIZURES IS PROPOSED

The American Clinical Neurophysiology Society (ACNS) defines a neonatal seizure as a "sudden, abnormal EEG event, defined by a repetitive and evolving pattern with a minimum 2 μV peak-to-peak voltage and duration of at least 10 seconds."[4] This definition—specifically including the 10-second minimum duration—has since been adopted for critically ill

children and adults.[5] For neonates, evolving EEG patterns that are less than 10 second in duration have been labeled brief rhythmic discharges (BRDs). However, the present ILAE position paper eliminates the 10-second rule from the seizure definition.

Although the 10-s cutoff was certainly arbitrary, it was widely accepted and formed the basis for decades of work on neonatal seizures. The challenge of eliminating the duration from the neonatal seizure definition is that it hinders our ability to directly apply the current literature to bedside clinical care; recent studies have consistently defined an EEG seizure as at least 10 seconds in duration.[6–11] We do not know how the published data apply to seizures that last less than 10 seconds. This change will also introduce potentially significant variability to future studies. Will some researchers and clinicians retain the "old" 10-second rule, whereas others remove the duration from their EEG interpretation and seizure diagnoses? How will seizure duration inform treatment decisions? These questions are currently unanswered and will be challenging to address.

A compromise of defining BRDs as "possible brief seizures" and highlighting the need for further study may have been more straightforward and motivated focused research on seizure burden. I agree with the task force that although "BRDs are considered to be electrographically distinct from neonatal seizures, in practice they indicate pathology and often co-occur with electrographic seizures."[3] This does not mean that, based upon today's evidence, BRDs should be considered seizures and treated as such. This area of controversy must be addressed as new studies of neonatal seizures are designed, current studies are reported, and existing data are interpreted in the present clinical context.

4 | STATUS EPILEPTICUS IS NOT INCLUDED IN THE NEW CLASSIFICATION

The task force concluded that status epilepticus could not be included in the present report, because there is not an agreed-upon definition. However, the ACNS defined neonatal status epilepticus nearly 10 years ago as "the summed duration of seizures comprises >50% of an arbitrarily defined 1-hour epoch. In other words, if half or more of any given hour of recording shows seizures, then status epilepticus exists for that epoch."[12] This definition has been widely accepted by the neonatal neurology community (e.g., Nash et al.,[13] Wusthoff et al.[14]) and associated with outcomes after neonatal seizures (e.g., Glass et al.,[15] Uria-Avellanal et al.,[16] Glass et al.[17]).

5 | THE FIRST AND MOST IMPORTANT ETIOLOGIC DISTINCTION MUST BE BETWEEN ACUTE PROVOKED SEIZURES AND EPILEPSY

The task force has mapped neonatal seizure etiologies onto the framework of the 2017 report (developed for older children and adults).[2] This is appealing for its simplicity. However, it ignores a critical and clinically essential distinction: acute provoked neonatal seizures must be addressed differently from seizures that are manifestations of neonatal onset epilepsies. Without this distinction, the etiologic classification is meaningless. As an example, neonates with perinatal stroke often have acute provoked seizures, but only sometimes go on to develop epilepsy after a latent period of months or years. For such infants, it may be appropriate to discontinue antiseizure medications once the acute flurry of seizures subsides. Conversely, neonates with seizures due to structural brain malformations have epilepsy. These infants need evaluation and long-term treatment plans directed at their epilepsy. In the current proposal, both groups of infants (those with perinatal stroke and acute provoked seizures and those with seizures due to brain malformation) are lumped into the "structural neonatal seizure" category. It must be underscored that before the etiology category is considered, the nature of the seizures (acute provoked seizures vs. manifestations of epilepsy) must be established.

The neonatal neurology community should applaud the ILAE for bringing neonatal seizures into the fold with this new modification of the classification of seizures and the epilepsies. As with previous classification proposals, the current document is not the end of the story. There remain several key areas of controversy and uncertainty in this field. However, the most important takeaway is that seizures in neonates are now explicitly defined by their EEG signature—a major and positive advance. Next steps include alignment of definitions across professional organizations (e.g., ILAE and ACNS), application of uniform definitions of seizures and status epilepticus to research protocols, and always being certain (in clinical practice and for research purposes) to distinguish newborns with acute provoked seizures from those with neonatal onset epilepsy.

CONFLICT OF INTEREST

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