The International League Against Epilepsy New Classification of Neonatal Seizures

Eli M. Mizrahi [a], MD, Ronit M. Pressler [b], MD on behalf of the Task Force on Neonatal Seizures, Commission on Classification and Terminology, International League Against Epilepsy (ILAE)*

Affiliations

[a] Departments of Neurology and Pediatrics, Baylor College of Medicine, Houston, TX, USA

[b] Clinical Neuroscience, UCL-Great Ormond Street Institute of Child Health and Department of Clinical Neurophysiology, Great Ormond Street Hospital for Children, NHS Foundation Trust, London, UK

*Members of the ILAE Task Force are listed in the Acknowledgements

Correspondence

Eli M. Mizrahi, MD
Chair, Department of Neurology
Professor of Neurology and Pediatrics
James A. Quigley Endowed Chair in Pediatric Neurology
7200 Cambridge Street
MS: BCM609
Houston, TX 77030
emizrahi@bcm.edu

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Abbreviations:

aEEG amplitude integrated electroencephalogram

cEEG continuous electroencephalogram

EEG Electroencephalogram

ILAE International League Against Epilepsy

Contributors' Statement Page

Dr. Mizrahi and Dr. Pressler conceptualized this paper based upon the previously published report of the Task Force on Neonatal Seizures, Commission on Classification and Terminology, International League Against Epilepsy (ILAE), in which they both participated (Dr. Pressler served as Chair). They drafted the initial manuscript and reviewed and revised the final manuscript. Drs. Mizrahi and Pressler approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Introduction

Clinical recognition has been the cornerstone of diagnosis and management of neonatal seizures from the earliest days of care for affected infants and previous classification systems have been based upon these bedside observations. Recently, the Task Force on Neonatal Seizures of the International League Against Epilepsy (ILAE) published a new classification system that has significant implications for the care of newborns suspected of seizures. This new construct includes electroencephalographic (EEG) confirmation rather than reliance solely on clinical observation of seizures **(1).** For some newborns it will improve diagnosis and management that may affect long-term neurodevelopmental outcome. For others, it may emphasize additional disparities in health care requiring new clinical strategies. Here we discuss the rationale for the development of this new classification, advantages and limitations, potential impact, and new strategies for resource-challenged care centers.

Rationale and methodology

Historically, efforts to characterize and classify neonatal seizures have been relatively independent from considerations of seizures and epilepsies of older children and adults with the understanding that the immature brain manifests clinical events of epileptic origin differently than the more developed brain. Recently, the ILAE published a new classification for seizures of older children and adults and questioned whether neonatal seizures could be considered within that newly adopted framework **(2)**. A Task Force was established comprised of international experts (listed in acknowledgements) who followed the ILAE protocol for development of new clinical guidelines **(1).**

Previous classifications of neonatal seizures were based upon contemporary methodology: clinical observation only, routine (short-term) EEG, EEG-video recordings, and continuous EEG (cEEG) monitoring. Underlying these efforts was the fundamental assumption that the clinical seizure was the biomarker for associated electrographic seizures considered to be detrimental to the developing brain if left unchecked (**3**).

The findings showed: some clinical features were unique to the neonatal period; some were similar to those of older children; some occurred with a consistent EEG discharge (electroclinical seizures); some clinical events occurred without any EEG signature (clinical-only); and some electrographic seizures occurred without any accompanying clinical events (electrographic-only or subclinical) **(4).** EEG-video studies demonstrated that clinical recognition is unreliable in identifying seizures consistently associated with electrographic events **(5)** and that more than 50% of neonatal seizures are electrographic-only (subclinical) (**4**). These findings have prompted reliance on cEEG monitoring to provide seizure surveillance and assess electrographic seizure burden. It has been suggested that the degree of electrographic seizure burden (independent of associated clinical manifestations) may adversely affect long-term neurodevelopmental outcome **(3).** More recently it has been suggested that early diagnosis with EEG monitoring may improve treatment success (**6**).

Classification and applications

This new ILAE classification is based upon recognition of electrographic seizure activity; categorized as electroclinical or electrographic-only (**Figure 1**). The initial application of this classification is the identification of infants who either may be considered at risk for developing seizures or who have been observed experiencing abnormal clinical events suspected of being seizures. This would prompt the institution of EEG (either routine EEG or cEEG monitoring

with video) or, if not available, amplitude-integrated EEG (aEEG) for seizure surveillance, diagnosis and subsequent management. In this classification, the critical EEG finding is electrographic seizure activity; interictal or post-ictal findings are not used to characterize clinical events observed prior to monitoring.

The clinical features of the electroclinical events are classified as: motor, non-motor, sequential (multiple consecutive clinical features during a given seizure), or unclassified. Motor events are classified as: automatisms, clonic, epileptic spasms, myoclonic, tonic. Non-motor events are classified as: autonomic and behavioral arrest. In addition, a clinical framework is proposed that is consistent with the ILAE classification of seizures and epilepsies of older children and adults describing the relationship of etiologies and co-morbidities to seizure types and subsequent neonatal epilepsy syndromes (**1**).

Advantages and limitations

This classification provides precision for diagnosis and management by utilizing EEG as a biomarker for these events; whether electroclinical or electrographic-only. With this approach a significant proportion of seizures (electrographic-only) that otherwise would go undetected will be diagnosed and potentially treated. In addition, some seizure types may indicate a certain etiology and therapeutic strategies can be tailored to start treatment early and reduce electrographic seizure burden (**6**). The classification may also refine the characterization of the wide range of motor and non-motor seizure manifestations, allowing greater accuracy in diagnosis compared to clinical observation (**4, 5**). It also can be a foundation for more standardized clinical trials of new therapies – an important goal since current treatments fall short of full seizure control.

The classification also has limitations since it is based upon the availability of EEG or aEEG. While available in many high-resource neonatal center, accessibility maybe still problematic in some hospitals and not often available globally in resource-limited areas. The ILAE recognizes that while the classification will improve health care for some, it underscores the need for EEG to achieve this goal. This may also uncover health care disparities in low-resource settings where up to one-half of seizures may go unrecognized and thus untreated, while other clinical events may be mischaracterized as seizures and receive unwarranted anti-seizure medication.

Impact on care and new strategies

The successful application of this classification requires new strategies in health care for neonates: a shift from clinical observation for seizure surveillance to the identification of infants with risk factors for developing seizures. Monitoring at-risk infants can determine electrographically confirmed seizures and exclude clinical events not of epileptic origin. Protocols for defining those at-risk infants may be individualized by respective institutions although have been suggested by the American Clinical Neurophysiology Society **(5)**. In addition, the duration of monitoring of at-risk infants is also currently variable, although 24 hours is usually considered to be an acceptable duration for screening for seizures (**6**).

Levels of diagnostic certainty (**Figure 2)** have been proposed based upon availability of EEG. With either EEG or aEEG there are two levels of certainty: **Level 1** –definite seizure (seizures confirmed by EEG with or without clinical manifestations); **Level 2a** – probable seizure (clinically identified as focal clonic or focal tonic seizures confirmed with aEEG). Without EEG or aEEG: **Level 2b** – probable seizure (focal clonic or focal tonic seizures observed by experienced clinical personnel); **Level 3** – possible seizure (other seizure types

observed by experience clinical personnel). The additional **Levels** (**4** and **5**) are those with either insufficient or negative (not considered seizures of epileptic origin) data.

This application is helpful in clinical management where EEG is not available: the clinical recognition of clinical events with greatest diagnostic certainty such as focal clonic and focal tonic seizure require treatment with anti-seizure medications while isolated automatisms or isolated autonomic events are not seizures and should not be treated. This strategy also includes staff training to enhance recognition of various types of clinical events. In addition, advocacy at the institutional level to improve availability of EEG/aEEG is an important strategic goal.

Conclusion

This new ILAE classification of neonatal seizures shifts seizure diagnosis and on-going surveillance from clinical observation to EEG recording, allowing greater accuracy in detection of electroclinical and electrographic-only seizures. It provides greater precision in treating confirmed seizures and preventing unnecessary treatment for clinical events determined to be of non-epileptic origin. The classification is a new tool for both advancing investigations and refining practice parameters of affected infants.

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Additional members of the Task Force on Neonatal Seizures, Commission on Classification and Terminology, International League Against Epilepsy (alphabetically): **Maria Roberta Cilio, MD**, Division of Pediatric Neurology, Institute for Experimental and Clinical Research, Saint-Luc University Hospital, Université Catholique de Louvain, Brussels, Belgium; **Linda S. de Vries, MD**, Department of Neonatology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; **Solomon L. Moshé, MD**, Isabelle Rapin Division of Child Neurology, Saul R. Korey Department of Neurology, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA; **Magda L. Nunes, MD**, Pontificia Universidade Catolica do Rio Grande do Sul - PUCRS School of Medicine and the Brain Institute, Porto Alegre, RS, Brazil; **Perrine Plouin, MD**, Department of Clinical Neurophysiology, Hospital Necker Enfant Malades, Paris, France; **Chahnez C. Triki, MD**, Department of Child Neurology, Hedi Chaker Hospital, LR19ES15 Sfax University Stax, Tunisia; **Sampsa Vanhatalo, MD**, Department of Clinical Neurophysiology and BABA center Children's Hospital, HUS Imaging, Neuroscience Center, Helsinki Institute of Life Science, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland; **Kollencheri Puthenveetil Vinayan, MD**, Department of Pediatric Neurology, Amrita Institute of Medical Sciences, Cochin Kerala, India; **Jo M. Wilmshurst, MD**, Department of Paediatric Neurology, Red Cross War Memorial Children's Hospital, Neuroscience Institute, University of Cape Town Cape Town, South Africa; **Hitoshi Yamatomo, MD**, Department of Pediatrics, St. Marianna University School of Medicine Kawasaki, Japan; **Elissa Yozawitz, MD**, Isabelle Rapin Division of Child Neurology, Saul R. Korey Department of Neurology, Albert Einstein College of Medicine and Montefiore Medical Center, Bronx, NY, USA; **Sameer M. Zuberi, MD**, Paediatric Neurosciences Research Group, Royal Hospital for Children & Institute of Health & Wellbeing, University of Glasgow Glasgow, UK.

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Figure 1. Diagnostic framework of seizures in the neonatal period including classification of seizures. Reprinted with permission (**1**). The electro-clinical listing represents the classification of clinical neonatal seizures.

Figure 2. Algorithm to determine degrees of diagnostic certainties for neonatal seizures. This flow chart considers the diagnostic certainty of events being neonatal seizures depending on the available diagnostic method (EEG, aEEG or observation by experienced personnel) and seizure type. Level 5 events are included since that may be initially thought to have clinical features suggestive of seizures of epileptic origin, but with cEEG or aEEG are shown not to be. Reprinted with permission (**1**).