Comment on the 2018 proposal of a new classification of neonatal seizures by the ILAE task force

Coordinated by Monika Eisermann (France)
Contributions by Thomas Bast (Germany), Lucia Fusco (Italy), Anna Kaminska (France), Marie-Dominique Lamblin (France), Rima Nabbout (France).

Purpose of a new classification proposal is greater ease of communication among clinicians (experts in the domain, other subspecialties), nonmedical community, researchers, and also patients. Conceptional clarity is of great clinical importance but getting all expert opinions and remarks embedded into one single classification is an effortful, perhaps immeasurable or impossible task. Therefore we deeply congratulate the task force members for their hard work and their excellent proposal in this challenging domain of Neonatal Seizure Classification where reality is so complex.

POINTS OF AGREEMENT

Video-EEG as the gold standard
The recommendation of video-EEG as the gold standard in neonatal seizure diagnosis and classification is very important. There is a significant difference compared to older children and adults in whom diagnosis is often based on seizure history and semiology and ictal and interictal EEG. It is however unclear why in the framework schema « video-EEG/aEEG » are displayed side by side in the box. This leads to falsely believe in a comparable value of both techniques however video-EEG is rightly stated to be the gold standard. It would therefore be preferable to display only « video-EEG/EEG », eventually (aEEG) in parentheses.

Term « electrographic only »
The inclusion of « electrographic only » seizures is very important as these are frequent, and burden and consequences have been demonstrated to be equal to electro-clinical seizures. However a more precise description of the ictal electroencephalographic patterns as frequencies, periodicities, amplitudes, aspects (i.e. high amplitude rhythmic delta waves in premature, periodic delta or theta waves superimposed or not by fast rhythms, electro decrement, very low amplitude rhythmic patterns) and their localization and propagation pattern is crucial in terms of etiological considerations, treatment choice and the learning about the pathophysiology as seizure generation structures, specific brain circuits or seizure control structures in the immature brain.

Minimal length of discharge duration 10 seconds
The renouncement of the arbitrary minimal duration of 10 seconds (for some authors even 20 seconds) to allow the diagnosis of a seizure event is appreciated, as shorter discharges may also be an indicator of epileptic neuronal networks in the newborn, and no study had evaluated the appropriateness of these definitional limits. In contrast, it has been demonstrated that shorter (5-10 s) paroxysmal EEG changes in term newborns (Nagarajan 2011) were significantly associated with an increased mortality, morbidity and EEG background anomalies, similar to conventional seizures (> 10 s with or without clinical signs). However the acronym BIRDs (brief interictal rhythmic discharges) may
lead to misunderstanding, and the previously used term BERDs (brief electroencephalography rhythmic discharges) may be preferable. The authors’ proposal for definition of seizures in the neonatal period as “an electrographic event with a pattern characterized by sudden, repetitive, evolving stereotyped waveforms with a beginning and an end” is acceptable. We agree that no minimum amplitude of the EEG pattern is needed as stated in the recommendations of the American Clinical Neurophysiology Society.

**Classification of neonatal seizures according to behavior versus electrographic**
We agree with the statement: “Clinical events without abnormalities on EEG are not actual seizures”. Some authors criticize that clinical seizures might be underdiagnosed in this classification because subcortical sites of injury may initiate seizures in neonates and preterms. However whether clinical signs as i.e. motor automatisms or hypermotor behavior not accompanied by EEG discharge might have a subcortical electrical correlate is at present neither provable nor disprovable. Moreover it is questionable if anti-seizure drugs would be efficient on these subcortically generated events.

**Focal/generalized seizures**
The opinion that there is no need to distinguish focal and generalized seizures in the neonatal period where all seizures are considered of focal origin, is acceptable. However it has to be kept in mind that in rare conditions seizure types in the neonate seem to rapidly engage bilaterally distributed networks as myoclonic jerks in early myoclonic encephalopathy as i.e. in glycine encephalopathy.

**Awareness/motor atonic and hyperkinetic/non-motor cognitive, emotional and sensory seizures**
As awareness and non-motor cognitive, emotional or sensory symptoms cannot be estimated as well as eventual atonic components due to the lying position in the neonate there is no argument to maintain them in the classification.

**POINTS OF DISCUSSION**

**Classification according to the predominant clinical feature**
We hear the authors’ argument about their decision to modify the 2017 seizure classification where the initial symptom is decisive, into the predominant symptom that is decisive. Their main argument is that classifying seizures according to the predominant clinical manifestations “is more likely to have clinical implications for etiology than determination of the seizure onset zone”. However literature arguments are not developed (no reference is provided), the population reviewed is small, and statistical analysis is not stated in table 4.

Moreover how to decide which is the predominant sign: the longest lasting sign or the most intensive/eye catching sign? Also the “less important/not predominating” symptom will disappear and important information and details will get lost.

We understand that most neonatal seizures are acute symptomatic seizures and complex seizure patterns are mainly observed in neonatal onset epilepsies and neonatal encephalopathies with seizures which are rare, and that the simplified classification can easily be used by less experienced caregivers. However phenotyping remains a crucial
part in seizures and epilepsies in the neonate.

**Seizure type motor sequential**
The information on the initial electroclinical aspect of a seizure and its further evolution/propagation pattern is of extreme importance, not only concerning etiological consideration and treatment decision, but also concerning the learning about the pathophysiology as seizure generation structures, specific brain circuits or seizure control structures in the immature brain. However a more detailed characterization of the succeeding electro-clinical aspects would be very important. There is i.e. a significant difference between a sequence of symptoms due to common propagation patterns (behavior arrest followed by focal clonic possibly bilateral clonic manifestations) or the coexistence of several seizures/seizure types within one ictal episode (unilateral body tonic contraction followed by myoclonic axial jerks and/or eyelid myoclonias, and then contralateral tonic posturing and finally focal clonic jerks). Moreover is difficult to understand why this seizure type is classified as a subgroup of the motor seizures and not as a separate seizure type, because sequential ictal symptomatology can also be observed (however rare) in exclusively non-motor seizures (i.e. behavioral arrest followed by autonomic symptoms) or in non-motor-motor seizures (i.e. behavioral arrest followed by cluster of spasms).

**Modifiers**
It is not clear why this expression has been chosen as it is confusing and gives the impression it will modify/change the seizure type, however it defines it more precisely. No “modifiers” are mentioned for electrographic seizures only. However distinguishing the ictal EEG pattern (see above) and their focal, multifocal, migrating etc. aspect is important concerning etiological considerations, treatment choice and prognosis.

**Conclusion**

*We deeply congratulate the task force members for their hard work and their excellent proposal in this challenging domain of Neonatal Seizure Classification where reality is so complex. Altogether the new classification of neonatal seizures is a very important advance and will significantly facilitate communication. The classification scheme is reasonably reduced to the relevant clinical seizure types in the neonatal period and, on the other hand, extended to pure electrographic seizures. However several issues need to be discussed, mainly the introduction of the seizure type sequential seizure and the classification according to the predominant clinical symptom in seizures with more than one co-existing clinical signs, where important information necessary for precise phenotyping will get lost. Also, the correlation between the predominant seizure symptom and the underlying etiology needs validation.*