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Editorial

Detecting neonatal seizures: A challenge accepted!

See Article, pages 1533–1540

1. Neonatal seizures – the clinical impact

The newborn brain is highly susceptible to epileptic seizures and the neonatal period is therefore one with the highest incidence of seizures throughout the life time. The occurrence of seizures within the first month is estimated at about 2–5 per 1000 live births and increases to up to 50% in high-risk populations such as extremely premature infants (Lanska and Lanska, 1996; Clancy, 2006). Neonatal seizures can be caused by a wide variety of underlying diseases, but ischemic insults, intra-cerebral hemorrhage and perinatal asphyxia resulting in hypoxic ischemic encephalopathy are the most common underlying diseases (Tekgul et al., 2006). Rare causes include hypoglycemia, neonatal infections and a wide variety of metabolic disorders all of which are important to recognize, as early treatment of the underlying disease may have a larger impact on prognosis than treatment of seizures themselves (Glass and Wirrell, 2009).

Mortality rates and neurodevelopmental outcome of infants with seizures is clearly linked to etiology, while a direct link between seizure burden and outcome is a subject of ongoing debates (Silverstein and Jensen, 2007). Several studies could show a clear link between the amount of seizures and severe clinical symptoms, disturbed EEG background activity, increased brain damage assessed on MRI and a poor neurological outcome (McBride et al., 2000; Björkman et al., 2010; Shah et al., 2014). Nevertheless it remains unclear whether there is a causal correlation between seizure and outcome or whether seizures themselves and their duration result in additional brain injury (Glass et al., 2009, 2011; Kwon et al., 2011). Studies trying to assess a causal relationship are rare. It may seem hard to imagine that repetitive seizures do not affect the immature brain structures especially in a critically ill newborn and thus it has been hypothesized that seizures might aggravate existing brain damage by increasing metabolic demand (Silverstein and Jensen, 2007). Miller and coworkers found evidence for disturbances in brain metabolism likely caused by seizures using MR spectroscopy (Miller et al., 2002).

If seizures increase neurological damage in affected children, early prevention or at least recognition is an essential key to care of infants at risk. Unfortunately despite all of the advances in perinatal medicine and the development of new technologies and medications, recognizing and treating seizures is still a major challenge even in modern ICU settings.

Reliable clinical recognition of neonatal seizures has proven to be a nearly unsolvable task even for trained personnel. Murray and coworkers demonstrated in an ICU setting with trained nurses and clinicians that as few as 27% of suspected seizures actually were accompanied by electrographic changes. In contrast only 9% of seizures seen on EEG had clinical symptoms which were recognized by the attending staff (Murray et al., 2008). One important reason for these low numbers is the increased electro-clinical dissociation which results in up to 70% electrographic seizure without clinical correlate (Murray et al., 2008). But even in seizures with clinical manifestations diagnosis without EEG is very difficult, as newborns especially critically ill ones experience many paroxysmal movements such as myoclonus and jittering that mimic seizure activity (Malone et al., 2009; Wusthoff, 2013). The striking clinical importance of identifying neonatal seizures and the major challenges which prevent it in clinical routine have led to various approaches of closing the diagnostic gap. The following paragraph will give a short overview of current methods requiring different degrees of technical and financial resources as well as clinical expertise.

2. Current methods of seizure detection and seizure identification

In an ICU setting in principle two EEG types are routinely recorded, conventional EEG and amplitude integrated EEG (aEEG). Depending on the head size conventional EEG might be recorded according to the international 10–20 system or with a reduced montage of ten electrodes (Wusthoff et al., 2009). Ideally EEG is recorded with simultaneous video. Conventional EEG has the highest spatial resolution of the discussed methods and is least likely to miss subtle and short epileptic seizures. Recording time is however limited by practicality as recording depends on trained technicians to maintain good EEG quality and on expert review. The technique thus has limited value for bed-side monitoring on most of the neonatal wards and the shorter the conventional EEG the higher the likelihood of underdiagnosing seizures.

AEEG has therefore become an increasingly used tool for high risk neonates. The processed and time compressed EEG allows pattern recognition by staff that is otherwise untrained in reading EEG (Viniker et al., 1984; Hellström-Westas and Rosén, 2006). While aEEG in principle is easy to apply and read, research has clearly shown that its value for seizure identification is largely dependent the approach used for recording aEEG traces. The easiest method of using two frontal electrodes from which aEEG tracings are calculated has proven to be less sensitive and specific for seizure recognition than methods using sets of parietal electrodes (Wusthoff et al., 2009), two independent electrode sets for each hemisphere

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and accompanying traces of raw EEG for verifying EEG patterns (Shah et al., 2008). The approach of combining aEEG with traces of raw EEG provides the highest sensitivity and specificity for identifying seizures and several automatic seizure detectors are on the market to facilitate identification (Shah et al., 2008).

Detecting seizure on video instead of EEG is a completely different approach to close the diagnostic gap (Kilbride et al., 2009; Kouamou et al., 2012). Of course this method is blind to seizure without clinical correlate and might only detect the tip of the iceberg when it comes to seizure activity (Murray et al., 2008). Nevertheless it is the least invasive method of continuous monitoring and combined with an automatic detection of suspect movement largely reduced the necessary resources for monitoring (Karayiannis et al., 2006a). As such it might be useful as a screening method in high risk infants, especially if the alternative is to rely on visual recognition by staff only. Detected and suspected seizure activity might then be confirmed by any of the above suggested EEG methods. Focal clonic movements are the most frequent clinical sign of seizures (Nagarajan et al., 2012). Karayiannis and coworkers have published a series of papers with elaborate methods trying to automatically detect video-taped seizures (Karayiannis et al., 2006a, 2006b). Using an approach in which neuronal networks learned feature recognition they were able to distinguish between myoclonic seizures, focal clonic seizures and random infant movement with a sensitivity and specificity above 90%.

3. What is new in this issue?

In the current issue of Clinical Neurophysiology, Pisani and coworkers apply a different approach of automated video seizure detection by Kouamou to a clinical cohort of neonates with and without seizures (Kouamou et al., 2012; Pisani et al., 2014). This approach fascinates with a striking simplicity to tackle the complicated business of seizure detection. Seemingly following the famous quote of Confucius "Life is really simple, but we insist on making it complicated" the paper bases its algorithm on relatively straight forward steps of video post processing which are illustrated in Figure 2 of Pisani et al. (2014). First images are converted to grey-scale and motion is quantified in consecutive time windows of the original video based on luminance changes. A global measure of motion is then computed as the simple sum of binarized luminance differences, with a prior erosion step for noise reduction. Up to this point the methods would detect any type of motion of the infant and thus analysis has to be followed by an automated interpretation of the detected motion. The key idea is that clonic seizures express a more periodic movement than all other random movements of the neonate and that the changes in movement over time can be used to correctly identify movements with high periodicity. The authors use ROC curves to demonstrate how the choice of consecutive windows within their video process and changes in overlap between the sequences influence the sensitivity and specificity their detection algorithm. The authors conclude that a balance between sensitivity with 71% and specificity with 69% for distinguishing seizures form random movement is best when analyzing periodicity of movement across two consecutive overlapped windows. These results are of course far from perfect and lower than those obtained in detection algorithms based on other modalities. The strength of the approach lies in its simple utilization as well as flexibility. ROC curves suggest that the parameters can be adjusted toward very high sensitivity values, which may be the key for using the method as a video screening tool in an ICU setting. As the method does not rely on high definition video or detailed color images its use is feasible even under circumstances of minimal handling and low resources. Moreover video-detection tools might reduce errors that occur if seizure recognition is based on visual recognition by staff only, videos could be used for training and cover times in which direct observation is not possible.

4. Where to go from here?

The diagnostic gap for neonatal seizures is a challenge, but it seems easy to handle in comparison to the treatment gap. In the same degree in which we know little about the effects of clinical and electrographic seizures on the neonatal brain we also do not know whether and which treatment will actually improve outcome in regard to mortality and neurological development (Glass et al., 2012; Roll et al., 2012). Randomized controlled trials are rare and only compare two medications at the same time (Booth and Evans, 2004). The question whether preventive treatment is possible remains unsolved (Hall et al., 1998). In contrast side effects of all treatment are well described and cannot be ignored (Stefovska et al., 2008; Glass and Wirrell, 2009). In a situation where the clinical impact of seizures and options for optimal treatment are uncertain to the described extent it seems hard to judge which tool is most appropriate for seizure recognition. Prior to each monitoring decision, gains from maximum seizure detection should be weighted against minimal stress for the infant and restricted ICU resources. The present video analysis will certainly not be able to detect all ictal events, but as suggested by the authors it might serve as a non-invasive screening tool and can be applied in combination with EEG recordings. Let's hope that knowledge about neonatal seizures, their consequences and treatment will soon advance to a stage in which is will be easier to define a gold standard for seizure recognition tools. Until then – as long as they are well validated – the research community profits from yet another idea to simplify a complex problem.

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