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EDITORIAL

Brain-focused care in the neonatal intensive care unit: the time has come☆,☆☆

Cuidado neurológico na unidade de terapia intensiva neonatal: chegou a hora

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Survival rates for extremely preterm infants and for critically ill term newborns have improved steadily over the last several decades; however, these same babies continue to experience high rates of adverse neurodevelopmental outcomes with life-long impact. Brain-focused care is a desired evolution in neonatal care after decades of focus on survival and extending the limits of viability. Neonatal neurology and neonatal neurocritical care are growing subspecialties that seek to better address the needs of neonates with, or at risk for, neurological compromise by integrating neonatal intensive care practices with focused neurologic care. The development and application of bedside neuromonitoring has significantly contributed to the enhanced focus and our ability to both monitor and provide care for these vulnerable newborns. Non-invasive neurologic monitoring with techniques such as amplitude-integrated electroencephalography (aEEG) and near-infrared spectroscopy (NIRS) allow screening and assessment at the bedside by neonatal nurses and physicians.

In this issue of the *Jornal de Pediatria*, Variane et al.[1] described a prospective cohort study of 23 preterm infants less than 31 weeks gestation and 17 term newborns with hypoxic ischemic encephalopathy (HIE). Subjects were monitored with aEEG with assessment of background activity, sleep–wake cycling (SWC), and presence of seizures on days 1, 2, and 3 of life. In the preterm group, abnormal background pattern and absence of SWC were the aEEG findings associated with death or severe abnormalities on cranial ultrasound. Abnormal background pattern was defined as discontinuous low-voltage, burst suppression, continuous low voltage, or flat tracing. In the term HIE group, seizures and longer time to normal background tracing were the aEEG features associated with death and MRI abnormalities.

The research findings presented by Variane et al.[1] add to a growing body of evidence supporting the use of aEEG in the neonatal intensive care unit. aEEG was first developed as a tool to assess the depth of anesthesia during surgery, providing real-time assessment of brain activity during exposure to anesthetic agents. aEEG monitoring devices now display both a limited channel EEG as well as a time-compressed aEEG trace allowing evaluation of background activity, displaying changes in background activity over time, and screening for seizures. The first background classification system, developed by Hellström-Westas, was based on pattern recognition to distinguish between five categories: continuous normal voltage, discontinuous normal voltage, burst suppression, continuous low voltage, and flat tracing.[2] Another classification method was developed by al Naqeeb based on simple voltage criteria.[3] A more consistent interpretation was found with the simple voltage criteria than with pattern recognition in one study[4]; however, the pattern

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recognition classification system remains widely used. aEEG has been shown to have good agreement with EEG background classification when studied in term newborns with HIE,[5] but no similar comparison has been performed in preterm infants. Term infants with neonatal encephalopathy were one of the first diagnostic groups to be studied with aEEG. Numerous early aEEG studies performed prior to use of therapeutic hypothermia determined that abnormal background patterns are a predictor of outcome in neonates with HIE. Accordingly, abnormal aEEG background pattern at less than 6 h of age was used as an eligibility criteria in several trials of therapeutic hypothermia for HIE.[6,7] Thoresen et al. performed an important study of continuous aEEG for 72 h in term infants with HIE in cooled ($n = 43$) and non-cooled ($n = 31$) newborns.[8] Recovery time to normal background pattern was found to be the best aEEG predictor of abnormal outcome at 18 months of age. In this analysis, normal background pattern included both continuous normal voltage and discontinuous normal voltage. Infants with a good outcome treated with normothermia had normal tracings by 24 h, whereas those treated with hypothermia had normal tracings by 48 h. Massaro confirmed the high positive predictive value of abnormal aEEG background for adverse outcome at hospital discharge.[9] SWC were present at the time of rewarming in 58% and all had a favorable outcome, while no babies with adverse outcome had SWC at the time of rewarming. A meta-analysis of eight studies in term infants with HIE concluded that aEEG had an overall sensitivity of 91% (95% CI: 87–95) and specificity of 88% (95% CI: 84–92) to predict poor outcome.[10] A recent meta-analysis of 31 aEEG studies concluded that burst suppression, continuous low voltage, and flat tracing are the aEEG background patterns that most accurately predict long term neurodevelopmental sequelae.[11]

Due to the high risk of neurodevelopmental impairment in extremely preterm infants, methods to assess the risk have been sought. The etiology of preterm brain injury is assumed to be multifactorial, including events in the peripartum period as well as acquired white matter injury, inflammation, and infections that may occur during hospitalization. Useful assessments have included clinical risk scores, neuroimaging, and early brain function. As neonatal brain function can be readily assessed using aEEG, it has been intensely investigated as a prognostic tool. Background pattern, SWC, and seizures have been used to prognosticate with several studies showing a good correlation with outcome.[12,13] A scoring system to objectively assess developmental maturation at increasing gestational and postnatal ages was developed by Burdjalov et al.[14] Their scoring system uses measures of continuity, presence of cyclic changes, degree of voltage amplitude depression, and bandwidth. The cycling score appeared to have the highest correlation with post-conceptual age and was felt to be the single best sign of cerebral maturity. A recent meta-analysis of the prognostic accuracy of early (within 7 days of life) aEEG or EEG to predict neurodevelopmental outcome at 1–10 years of age concluded that these measures have the potential to predict later neurodevelopmental outcome; however, there was substantial heterogeneity among studies with differing prognostic variables and outcomes.[15] They concluded that high-quality studies are needed to confirm these findings.

aEEG has several advantages over continuous EEG (cEEG) but it does not replace it as the gold standard for seizure diagnosis or for the evaluation of the EEG background brain activity. Due to the limited number of channels that are recorded (usually left and right parietal or central leads), aEEG is easy to apply without the need of an EEG technician. Favorable characteristics of aEEG include the following: aEEG is often available in clinical settings where full conventional EEG is not readily available; aEEG's lead application is easy to learn and is not a time-consuming procedure; aEEG can be used to monitor for long periods of time without burdening neurophysiologists, aEEG recording devices are easy to use and have a small bedside footprint; aEEG can be incorporated into the software of conventional EEG devices, allowing for simultaneous recording and display of the aEEG compressed trace as well as the full video-EEG; aEEG is easy to interpret with a pattern based classification system that parallels the classification of conventional EEG, but does not require extensive training in neurophysiology; and finally, the prognostic ability of aEEG may be superior to more subjective evaluations such as the neonatal neurologic exam. aEEG does have important limitations especially when being used to diagnose seizures. Due to the manner in which the signal is recorded and how the compressed aEEG trace is created, some seizures can be missed. First, aEEG only records EEG signal from a limited number of channels/regions of the brain. Seizures that arise in areas away from the recording leads may not be captured and therefore can be missed. In addition, seizures that are brief (<30 s) or low amplitude may be difficult to identify on the compressed trace. Using only the compressed aEEG trace to identify seizures results in low sensitivity and specificity for seizure recognition; therefore, both the compressed and raw traces should be evaluated.[16] Newer aEEG devices have incorporated seizure detection software to assist bedside clinicians in identifying seizures. Based on a survey of US neonatologists performed in 2012, 55% of neonatologists reported using aEEG in their practice. HIE and suspected seizures were the most common indications for use, and aEEG was primarily interpreted by neonatologists (87%).[17] Pediatric neurologists acknowledge the important role aEEG plays in the NICU to identify seizures and assess brain function. It lessens the demand for conventional video EEG, which is more costly, requiring specialized EEG technicians to perform the recordings and neurophysiologists for interpretation. Glass et al. encourage pediatric neurologists to learn aEEG interpretation in order to improve communication and care coordination at the bedside.[18]

Brain-focused care is now possible in NICUs equipped with neuromonitoring techniques such as aEEG and NIRS. The inevitable and critical question is whether the use of these neuromonitoring techniques will improve long-term neurodevelopmental outcomes. The wider use of aEEG has the potential to increase seizure identification, decrease seizure burden, and potentially minimize exposure to anticonvulsant medications by accurately identifying patients with electrographic seizures. Two recent investigations have dealt with the question of whether aggressive treatment of neonatal seizures decreases brain injury.[19,20] Van Rooij et al. found a significant relationship between seizure duration and MRI severity scores, supporting the assumption that seizures worsen existing brain injury.[19] A study by Srinvasakumar et al. compared newborns treated

for electrographic seizures to those treated for clinical seizures alone; seizure burden, MRI findings, and neurodevelopmental outcome were improved in the cohort with treatment of electrographic seizures.[20] We eagerly anticipate additional clinical studies using neuromonitoring techniques such as aEEG and NIRS that will provide us the evidence on how these technologies may be best used to optimize intensive care practices and lessen brain injury.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Variane GF, Magalhães M, Gasperine R, Alves HC, Scoppetta TL, Figueredo RJ, et al. Early amplitude-integrated electroencephalography for monitoring neonates at high risk for brain injury. J Pediatr (Rio J). 2017;93:460–6.
2. Hellström-Westas L, Rosén I, de Vries LS, Greisen G. Amplitude-integrated EEG classification and interpretation in preterm and term infants. NeoReviews. 2006;7:e76–87.
3. al Naqeeb N, Edwards AD, Cowan FM, Azzopardi D. Assessment of neonatal encephalopathy by amplitude-integrated electroencephalography. Pediatrics. 1999;103:1263–71.
4. Shellhaas RA, Gallagher PR, Clancy RR. Assessment of neonatal electroencephalography (EEG) background by conventional and two amplitude-integrated EEG classification systems. J Pediatr. 2008;153:369–74.
5. Hellström-Westas L. Comparison between tape-recorded and amplitude-integrated EEG monitoring in sick newborn infants. Acta Paediatr. 1992;81:812–9.
6. Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. N Engl J Med. 2009;361:1349–58.
7. Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, et al. Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. Lancet. 2005;365:663–70.
8. Thoresen M, Hellström-Westas L, Liu X, de Vries LS. Effect of hypothermia on amplitude-integrated electroencephalogram in infants with asphyxia. Pediatrics. 2010;126:e131–9.
9. Massaro AN, Tsuchida T, Kadom N, El-Dib M, Glass P, Baumgart S, et al. aEEG evolution during therapeutic hypothermia and prediction of NICU outcome in encephalopathic neonates. Neonatology. 2012;102:197–202.
10. Spitzmiller RE, Phillips T, Meinzen-Derr J, Hoath SB. Amplitude-integrated EEG is useful in predicting neurodevelopmental outcome in full-term infants with hypoxic-ischemic encephalopathy: a meta-analysis. J Child Neurol. 2007;22:1069–78.
11. Awal MA, Lai MM, Azemi G, Boashash B, Colditz PB. EEG background features that predict outcome in term neonates with hypoxic ischaemic encephalopathy: a structured review. Clin Neurophysiol. 2016;127:285–96.
12. Klebermass K, Olischar M, Waldhoer T, Fuiko R, Pollak A, Weninger M. Amplitude-integrated EEG pattern predicts further outcome in preterm infants. Pediatr Res. 2011;70:102–8.
13. Wikström S, Pupp IH, Rosén I, Norman E, Fellman V, Ley D, et al. Early single-channel aEEG/EEG predicts outcome in very preterm infants. Acta Paediatr. 2012;101:719–26.
14. Burdjalov VF, Baumgart S, Spitzer AR. Cerebral function monitoring: a new scoring system for the evaluation of brain maturation in neonates. Pediatrics. 2003;112:855–61.
15. Fogtmann EP, Plomgaard AM, Greisen G, Gluud C. Prognostic accuracy of electroencephalograms in preterm infants: a systematic review. Pediatrics. 2017:139, pii: e20161951.
16. Shellhaas RA, Soaita AI, Clancy RR. Sensitivity of amplitude-integrated electroencephalography for neonatal seizure detection. Pediatrics. 2007;120:770–7.
17. Shah NA, Van Meurs KP, Davis AS. Amplitude-integrated electroencephalography: a survey of practices in the United States. Am J Perinatol. 2015;32:755–60.
18. Glass HC, Wusthoff CJ, Shellhaas RA. Amplitude-integrated electro-encephalography: the child neurologist's perspective. J Child Neurol. 2013;28:1342–50.
19. van Rooij LG, Toet MC, van Huffelen AC, Groenendaal F, Laan W, Zecic A, et al. Effect of treatment of subclinical neonatal seizures detected with aEEG: randomized, controlled trial. Pediatrics. 2010;125:e358–66.
20. Srinivasakumar P, Zempel J, Trivedi S, Wallendorf M, Rao R, Smith B, et al. Treating EEG seizures in hypoxic ischemic encephalopathy: a randomized controlled trial. Pediatrics. 2015;136:e1302–9.