EARLY-ONSET NEONATAL SEIZURES – CLINICAL AND ETIOLOGICAL CONSIDERATIONS

Florina Doandes[1,2], Aniko Manea[1,2], Nicoleta Lungu[1,2], Daniela Cioboată[1,2], Oana Costescu[1,2], Marioara Boia[1,2]

Abstract

Seizures are more common in the neonatal period than in any other time of life, most of them occurring in the first week of life. Neonatal seizures frequently present just with subtle signs, or are entirely nonconvulsive, with no clinical manifestation and may be only detectable by electroencephalography (EEG), especially in ELBW preterm, due to neurological immaturity. Common causes of neonatal seizures include hypoxic ischaemic encephalopathy, intracranial haemorrhage, intracranial infections, congenital cerebral malformations, metabolic disorders, and focal ischaemic stroke. Neonatal hypoxic-ischemic encephalopathy (HIE) is a leading cause of long-term neurological morbidity and important cause of mortality.

Keywords: neonatal seizures, hypoxic-ischemic encephalopathy, neonatal encephalopathy.

Introduction

In early neonatal pathology, seizures often occurs isolated or associated with other neurological, metabolic or infectious diseases.

The so-called organic seizures, occurring on the substrate of a neuropathological lesion, are slow-evolution forms with imaging and electrical (EEG) changes, with different clinical expression depending on the degree of neurological maturity.

Perinatal hypoxic-ischemic encephalopathy is a common cause, all five neuropathological patterns being present: isolated and diffuse hypoxic lesions, periventricular leucomalacia, basal ganglion necrosis, selective neuronal lesions, parasagittal cerebral injury.

The role of APGAR score in appreciation and correlation with disease evolution is very discussed, as there are other pathologies with low APGAR score at birth: amniotic fluid aspiration, maternal infections, anesthetics administered to the mother, prematurity.

Neonatal seizures- clinical and etiological aspects

A seizure is defined clinically as a paroxysmal alteration in neurological function (behavioral, motor, or autonomic function). This definition includes paroxysmal alterations that are definitely epileptic, electro-clinical seizures, as well as clinical-only seizures. Electro-clinical seizures refers to their temporal association with EEG seizure activity, while paroxysmal clinical phenomena that are not consistently time-locked with EEG seizure patterns, define clinical-only seizures (1).

Clinical diagnosis of seizures is a major issue. There is a high incidence of EEG-only seizures in neonates (non-convulsive, subclinical, occult seizures). Numerous studies have indicated that about 80% of EEG seizures in neonates have no associated clinical symptoms, and therefore would not be identified without continuous EEG monitoring even by expert clinicians. Also, there are no differences in the degree of encephalopathy and the electroclinical seizures or EEG-only seizures (1,2).

It is very important to determine the etiology of neonatal seizures because of the significant impact on prognosis and outcome and influences further therapeutic strategies (3-5). The three most common etiologies of neonatal seizures are hypoxic-ischemic encephalopathy, ischemic stroke and intracranial hemorrhage (6). They are also a common manifestation of infection (meningitis, encephalitis), acut metabolic disorder (hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, hypernatremia) or inborn errors of metabolism (galactosemia, hyperglycinemia, urea cycle disorders).

Clinical manifestations are variables. Focal seizures consist of twitching of muscle groups, particulary those of the extremities and face. Many muscle groups simultaneously are involved in multifocal clonic seizures. Tonic seizures are characterized by rigid posturing of the extremities and trunk and are sometimes associated with fixed deviation of the eyes. Myoclonic seizures are brief focal or generalized jerks of the extremities or body (7). One particular type of neonatal seizures are so-called "subtle seizures", which are clinically manifested as chewing, pedaling or bicycling movements, ocular movements as blinking or nistagmus, apnea or excessive salivation.

Neonatal seizures are mostly focal. Generalized seizures have been described in rare instances, and their clinical presentation is highly variable.

[1]"Louis Turcanu" Children's Emergency Hospital, Neonatology Department, Timisoara, Romania
[2]"Victor Babes" University of Medicine and Pharmacy, Timisoara, Romania
E-mail: florina_doandes@yahoo.com, aniko180798@yahoo.com, nico_lungu2001@yahoo.com, daniela.cioboata@yahoo.com, oanabilav@yahoo.com, marianaboia@yahoo.com

Clinical seizures like focal seizures (clonic or tonic) and some myoclonic seizures have corresponding discharge on EEG, are clearly epileptic and are likely to respond to anticonvulsivant treatment. On the other side, generalized tonic seizures, subtle seizures and some myoclonic seizures, do not have activity recorded on the EEG. These infants tend to be neurologically depressed or comatose as a result of hypoxic-ischemic encephalopathy and may not require or respond to antiepileptics (8).

We can also meet electrical seizures, with markedly abnormal background EEG, without clinical seizures, in comatose infants who are not on anticonvulsivants. Conversely, electrical seizures may persist in patients with focal seizures after the introduction of anticonvulsivant treatment, without clinical signs (8).

The longterm EEG recording is the method commonly used to detect the presence of electrographic seizures. In the neonatal intensive care unit (NICU) amplitude integrated EEG (aEEG) technology is increasingly used for continuous monitoring of brain function. It is used independently or in conjunction with conventional EEG recording in NICU. Only clinical observation alone can under-diagnosis neonatal seizures, but also suspected episodes may not show corresponding electrographic evidence of seizures. Conventional EEG and aEEG are the two main methods used for detection and monitoring of the newborn infants (9).

Neonatal hypoxic-ischemic encephalopathy

Hypoxic-ischaemic brain injury remains a significant problem in our days, both in term and near-term infant.

Neonatal hypoxic-ischemic encephalopathy (HIE) is a leading cause of long-term neurological morbidity and important cause of mortality. The consequences are devastating as survivors present various neurodevelopmental problems, with financial, emotional and physical implications both for victims and their families.

According to Volpe (3), hypoxemia may be defined as the "diminished amount of oxygen in the blood supply", and cerebral ischemia is defined as the "diminished amount of blood perfusing the brain". The more important of the two forms of oxygen deprivation seems to be cerebral ischemia because it also leads to glucose deprivation.

The term HIE is often incorrectly used synonymously with neonatal encephalopathy (NE). NE is a clinical defined syndrome of disturbed neurological function in the earliest days of life in the full-term infant, manifested by difficulty with initiating and maintaining respiration, depression of tone and reflexes, subnormal level of consciousness and often seizures (7). Conditions causing neonatal depression and neonatal encephalopathy can mimic intrapartum asphyxia: congenital infections, neonatal sepsis, congenital myotonic disorders (myasthenia gravis, Prader–Willi syndrome, peroxisomal disorders), metabolic conditions (maple syrup urine disease), lung or airway disorders (pneumothorax, congenital diaphragmatic hernia), extracranial trauma causing significant blood loss and low blood pressure, genetic disorders associated with thrombotic or thrombophilic abnormalities (factor V Leiden deficiency, protein C and protein S deficiencies, anticardiolipin antibodies) (10).

If there is evidence that intrapartum asphyxia is the cause of the neonatal encephalopathy, the disorder is termed hypoxic–ischaemic encephalopathy (HIE).

Neonatal complications of intrapartum asphyxia include multiorgan failure and neonatal encephalopathy. Hypoxic-ischemic encephalopathy is the most studied clinical condition, producing the most serious sequelae.

Four essential criteria are necessary before acute intrapartum hypoxia insult can be considered to be the cause of a moderate to severe neonatal encephalopathy, that subsequently results in cerebral palsy (11):

1. Evidence of a metabolic acidosis in intrapartum fetal umbilical arterial cord or very early neonatal arterial blood samples (pH <7.00 and base deficit >/= 12 mmol/L);
2. Early onset of severe or moderate neonatal encephalopathy in infants born at 34 or more weeks of gestation;
3. Cerebral palsy of the spastic quadriplegic or dyskinetic type;
4. Exclusion of other etiologies (trauma, coagulation disorders, infectious conditions, genetic disorders).

Additional criteria, that together suggest an intrapartum timing but by themselves are not specific:

1. A sentinel hypoxic event occurring immediately before or during labour (prolapsed umbilical cord, uterine rupture, placental abruption, acute maternal haemorrhage, maternal anaphylaxis, acute neonatal haemorrhage);
2. Sudden, rapid and sustained deterioration of the fetal heart rate;
3. Apgar scores of 0-6 for longer than 5 minutes;
4. Early evidence of multisystem involvement (within 72 h of life);
5. Early imaging evidence of acute cerebral abnormality.

Sartan and Sartan developed the three-level grading system of mild, moderate and severe encephalopathy widely used, based on clinical symptoms and EEG (12,13).

Infants with the mildest degree of encephalopathy (stage 1) have transient irritability, hypertonia and poor feeding that usually lasts less than 24–48 hours. It is associated with a good neurological outcome.

Newborn infants with moderate encephalopathy (stage 2) show lethargy, hypotonia, hyporeflexia and seizures. The EEG typically shows reduced background activity associated with a lowering of the lower baseline on the amplitude integrated EEG with seizures. Seizures typically occur in moderate encephalopathy, with a poor outcome in 15–40% of the cases (10).

Stage 3 encephalopathy (severe) is characterized by profound stupor or coma and the EEG is usually isoelectric, suppressed or burst suppression. Infants are flaccid and unresponsive to any stimuli, often associate bradycardia, hypotension and apneea. Seizures are common and they are often refractory to anticonvulsants. The mortality rate is high and nearly all survivors develop sequelae.

Discussions

A study regarding prediction of neonatal seizures in HIE concluded that EEG variables performed better than clinical variables such as low Apgar scores and low cord pH, in encephalopathic neonates undergoing therapeutic hypothermia (14). HIE-seizures in neonates accompany high seizure burdens with frequent status epilepticus and electrographic seizures (15).

Among infants diagnosed with hypoxic-ischemic encephalopathy, the mortality and morbidity often attributed to neonatal seizures can be better explained by the underlying severity of encephalopathy. This are the conclusions of a study using the data collected from 208 infants diagnosed with hypoxic-ischemic encephalopathy, who were enrolled in an National Institute of Child Health and Human Development (NICHD) trial of hypothermia (16). It can be said that seizures are a symptom of underlying encephalopathy, and there is no evidence to suggest that seizures themselves cause long-term adverse neurological outcomes (17).

In a study of 426 neonates, Hannah C. Glass, Renée A. Shellhaas and colab. concluded that the most common seizure etiologies were hypoxic-ischemic encephalopathy (38%), ischemic stroke (18%), and intracranial hemorrhage (11%) (6).

HIE-seizures in neonates are known for their resistance to first-line antiepileptic drugs (AEDs) like Phenobarbital (18). The alternative treatment options for refractory seizures, such as levetiracetam and midazolam, have shown variable effects (18-20). Treating seizures may improve long-term neurodevelopmental outcomes, as clinical seizures in neonates with HIE are associated with worse neurodevelopmental outcomes, independent of the severity of HIE (21).

For treating neonates with HIE, therapeutic hypothermia has become a standard practice, based on the evidence from pre-clinical and clinical studies that documented reduced brain injury in HIE-neonates (22,23). Clinical studies have documented that therapeutic hypothermia significantly reduced mortality and short-term morbidity, and improved antiepileptic drugs efficacy in neonates with HIE (23–25).

Conclusions

The immature brain has a higher seizure susceptibility due to multiple developmentally regulated features (18,26).

80–85% of neonatal seizures are predominantly caused by hypoxic–ischemic encephalopathy (HIE), intraventricular hemorrhage, metabolic disturbances, and infections (18).

Clinical detection of neonatal seizures is difficult because not all the infants have clinical manifestations of seizures and the detection of them represents a particular diagnostic challenge in the neonatal intensive care unit (27,28).

Early diagnosis and appropriate treatment can reduce the long-term complications and sequelae.

References

1. Massey SL, Jensen FE, Abend NS. Electroencephalographic monitoring for seizure identification and prognosis in term neonates. Semin Fetal Neonatal Med. 2018;23(3):168–74.
2. R.R. Clancy, A. Legido and D. Lewis, Occult neonatalseizures,Epilepsia29(1988), 256–261
3. Volpe JJ. Neurology of the newborn. Saunders/Elsevier; 2008. 1094 p, 912p.
4. Lombroso CT. Neonatal seizures: gaps between the laboratory and the clinic. Epilepsia. 2007;48 Suppl 2:83–106.
5. Soul JS. Acute symptomatic seizures in term neonates: Etiologies and treatments. Semin Fetal Neonatal Med. 2018;23(3):183–90.
6. Glass HC, Shellhaas RA, Wusthoff CJ, Chang T, Abend NS, Chu CJ, et al. Contemporary Profile of Seizures in Neonates: A Prospective Cohort Study. J Pediatr. 2016 Jul 1;174:98–103.
7. Kliegman, Robert M.; Behrman, Richard E.; Jenson, Hal B.; Stanton BF. Nelson Textbook of Pediatrics, 18th Edition. Philadelphia PA Saunders/Elsevier. 2007.
8. Mikati MA, Hani AJ. Chapter 593 – Seizures in Childhood. Nelson Textb Pediatr. 2016.
9. Rakshasbhuvankar A, Paul S, Nagarajan L, Ghosh S, Rao S. Amplitude-integrated EEG for detection of neonatal seizures: A systematic review. Seizure. 2015;33:90–8.
10. Rennie, Janet M.; Robertson, NJ; Groenendaal F. Neurological problems in the newborn. In: Rennie and Roberton's Textbook of Neonatology. Elsevier; 2012. p. 1065–223.
11. Hankins GD., Speer M. Defining the pathogenesis and pathophysiology of neonatal encephalopathy and cerebral palsy. Obstet Gynecol. 2003 Sep 1;102(3):628–36.
12. de Vries LS, Jongmans MJ. Long-term outcome after neonatal hypoxic-ischaemic encephalopathy. Arch Dis Child - Fetal Neonatal Ed. 2010.
13. Sarnat HB, Sarnat MS. Neonatal Encephalopathy Following Fetal Distress: A Clinical and Electroencephalographic Study. Arch Neurol. 1976.
14. Jain S V., Mathur A, Srinivasakumar P, Wallendorf M, Culver JP, Zempel JM. Prediction of Neonatal Seizures in Hypoxic-Ischemic Encephalopathy Using Electroencephalograph Power Analyses. Pediatr Neurol. 2017 Feb 1;67:64–70.e2.
15. Lynch NE, Stevenson NJ, Livingstone V, Murphy BP, Rennie JM, Boylan GB. The temporal evolution of electrographic seizure burden in neonatal hypoxic ischemic encephalopathy. Epilepsia. 2012;
16. Kwon JM, Guillet R, Shankaran S, Laptook AR, McDonald SA, Ehrenkranz RA, et al. Clinical seizures in neonatal hypoxic-ischemic encephalopathy have no independent impact on neurodevelopmental outcome: Secondary analyses of data from the neonatal research

network hypothermia trial. J Child Neurol. 2011;
17. Shetty J. Neonatal seizures in hypoxic-ischaemic encephalopathy - risks and benefits of anticonvulsant therapy. Dev Med Child Neurol. 2015;
18. Kang SK, Kadam SD. Neonatal Seizures: Impact on Neurodevelopmental Outcomes. Front Pediatr. 2015;
19. Fürwentsches A, Bussmann C, Ramantani G, Ebinger F, Philippi H, Pöschl J, et al. Levetiracetam in the treatment of neonatal seizures: A pilot study. Seizure. 2010;
20. Castro Conde JR, Hernández Borges AA, Doménech Martínez E, González Campo C, Perera Soler R. Midazolam in neonatal seizures with no response to phenobarbital. Neurology. 2005;
21. Glass HC, Glidden D, Jeremy RJ, Barkovich AJ, Ferriero DM, Miller SP. Clinical Neonatal Seizures are Independently Associated with Outcome in Infants at Risk for Hypoxic-Ischemic Brain Injury. J Pediatr. 2009 Sep 1;155(3):318–23.
22. Burnsed JC, Chavez-Valdez R, Hossain MS, Kesavan K, Martin LJ, Zhang J, et al. Hypoxia-ischemia and therapeutic hypothermia in the neonatal mouse brain - A longitudinal study. PLoS One. 2015;
23. Azzopardi D, Strohm B, Marlow N, Brocklehurst P, Deierl A, Eddama O, et al. Effects of hypothermia for perinatal asphyxia on childhood outcomes. Obstetrical and Gynecological Survey. 2014.
24. Edwards AD, Brocklehurst P, Gunn AJ, Halliday H, Juszczak E, Levene M, et al. Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: Synthesis and meta-analysis of trial data. BMJ. 2010;
25. Shankaran S, Pappas A, McDonald SA, Vohr BR, Hintz SR, Yolton K, et al. Childhood outcomes after hypothermia for neonatal encephalopathy. Obstetrical and Gynecological Survey. 2012.
26. Jensen FE. Neonatal seizures: an update on mechanisms and management. Clin Perinatol. 2009;881–900.
27. Mizrahi EM. Neonatal seizures and neonatal epileptic syndromes. Neurologic Clinics. 2001.
28. Murray DM, Boylan GB, Ali I, Ryan CA, Murphy BP, Connolly S. Defining the gap between electrographic seizure burden, clinical expression and staff recognition of neonatal seizures. Arch Dis Child - Fetal Neonatal Ed. 2008 May 1;93(3):F187–91.

Correspondence to:

Aniko Manea
"Louis Turcanu" Children's Emergency Hospital,
Neonatology Department,
Iosif Nemoianu Street no. 2,
Timisoara,
Romania,
E-mail: aniko180798@yahoo.com