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Case Report

Challenges in diagnosis and treatment refractory neonatal seizures in immature brain

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ABSTRACT

Seizures are the most common clinical signs of neurologic dysfunction in neonates. The risk for seizures is inversely related to gestational age and birth weight. Several factors contribute to excessive excitation in the immature brain, such as depolarizing action of γ-aminobutyric acid, change of the subunit composition of the glutamate receptors and incomplete glial clearance of glutamate and potassium. Continuous EEG is the gold standard for diagnosing neonatal seizures. However, video EEG recording has several limitation, especially in preterm neonates. In recent years, amplitude-integrated EEG has been used to detect electrographic seizures. In accordance with the current recommendations, if neonatal seizures do not stop to phenobarbitone, levetiracetam or phenytoin may be used as a second-line anti-seizure medications, as well as midazolam or lidocaine. Midazolam is recommended in the treatment for refractory seizures in neonates requiring mechanical ventilation. In this report, we present a diagnostic and treatment dilemmas of refractory seizures in extremely preterm neonate.

Keywords: Anti-seizure medication, Electroencephalography, Neuromonitoring, Neonatal seizures, Preterm new-born

INTRODUCTION

Seizures are the most common clinical manifestation of neurologic dysfunction in neonates. The incidence to seizures is higher in the developing brain, during neonatal period. The risk for seizures is inversely related to gestational age and birth weight.[1,2] The more frequent occurrence of seizures in neonates, especially born preterm, is associated with the brain immaturity and the neurophysiological changes in function of receptors for neurotransmitters, such as γ-aminobutyric acid and glutamate.[3,4]

Structural brain lesions, such as periventricular-intraventricular hemorrhage and focal necrosis in white matter of the brain termed periventricular leukomalacia, are common causes of seizures in neonates born preterm. There are challenges to diagnose seizures in preterm neonates, because they may have many various repetitive movements which resemble seizures or have only electrographic seizures.[5] We report a diagnostic and treatment dilemmas of refractory seizures in extremely preterm neonate.

CASE REPORT

A 25 weeks of gestation male neonate was born by vaginal delivery to a 33-years-old primigravida mother, with a birth weight of 700 g and Apgar scores of 3 at first minute and 5 at five minutes after birth. Mother was diagnosed with thrombophilia, hypothyroidism, insulin resistance and chorioamnionitis.

The pregnancy was complicated by cervical incompetence treated with cervical stitch about two months before delivery. Also, the rupture of the fetal membranes occurred 6 days before delivery, so the mother received antibiotic therapy. After initial stabilization in the maternity ward,

the neonate was admitted to the institute of neonatology on the fourth day of life in severe condition. On the 7th day of life, the neonate had presented with clonic seizures followed by decreased in oxygen saturation. In neurological examination, the neonate had generalized hypotonia, symmetric spontaneous movements, primitive and deep tendon reflexes were absent. The seizures were treated with phenobarbitone. The cranial ultrasound showed subependymal hemorrhage and mild increase in echogenicity in the brain periventricular region. Video electroencephalography (EEG) showed irregularity of basic activity without epileptic discharges (Figure 1).

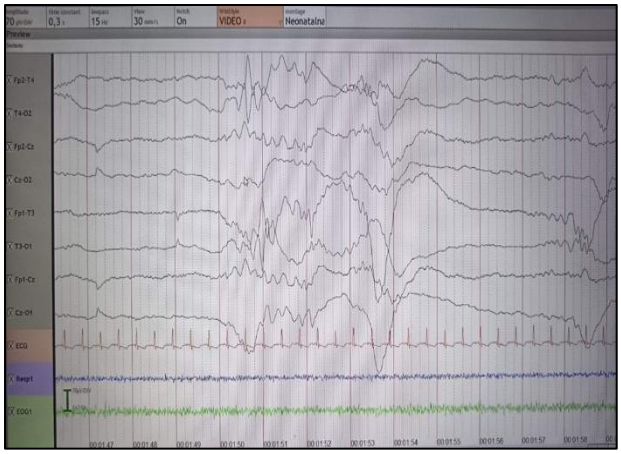

Figure 1: The interictal video EEG of extremely irregular discontinuous basic activity with periods of low-voltage basic activity and periods of high-voltage sharp wave bursts without epileptic discharges.

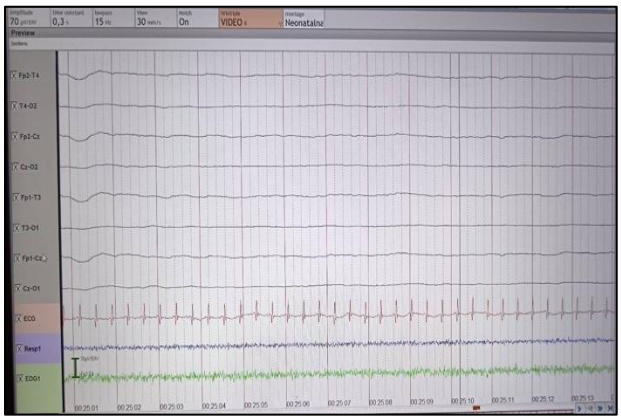

Figure 2: The video EEG in wakefulness of extremely low-voltage continuous basic activity without epileptic discharges.

At the age of one month, the neonate developed status epilepticus presented with bilateral symmetric and multifocal myoclonic seizures. At the same time, due to bilateral pneumonia, neonate required high fractions of inspired oxygen, high peak inspiratory pressure and high-frequency oscillatory ventilation (HFOV). Despite repeated doses of phenobarbitone up to the maximum daily dose (40 mg/kg/per day), the seizures persisted. Given the infant was on mechanical ventilation, continuous intravenous infusion of midazolam (0.2 mg/kg/h) was started with a gradual increase in dose to 0.4 mg/kg/h. Despite the use of phenobarbitone and midazolam, seizure control was not achieved, so levetiracetam was administered in one loading dose (40 mg/kg) and then continued in the maintenance dose intravenously.

Seizure control was achieved with the use of midazolam and levetiracetam. The midazolam was discontinued after 48 hours, so that further treatment of seizures was carried out with levetiracetam monotherapy. Transient electrolyte and metabolic disturbances, central nervous system (CNS) infections (bacterial meningitis, Herpes encephalitis) and structural brain lesions were excluded as the causes of refractory seizures. Video EEG showed depression of basic activity without epileptic discharges (Figure 2).

By the end of hospitalization, the neonate had no clinical and/or electrographic seizures and was discharged home without anti-seizure medication (ASM).

DISCUSSION

The incidence of seizures in neonates is higher than older children and adults. Neonatal seizures are seen in 1.5-3.5/1000 full-term neonates and 10-130/1000 preterm neonates.[6,7] Acute symptomatic seizures account for about 85% of neonatal seizures.[1,11]

Continuous EEG (cEEG) is the gold standard for diagnosing seizures in neonates.[8] However, the use of cEEG has several limitation, such as expensive equipment, EEG technician for application of electrodes and recording, as well as clinical neurophysiologist and epileptologist for EEG interpretation and to administer ASM accordance with ictal EEG finding. Also, additional challenges for use of cEEG in preterm neonates are smaller head size, reduced montages for EEG recording and potential pressure-induced damage of vulnerable skalp skin by electrodes.

Other factors that may delay ictal EEG recording include severe respiratory and hemodynamic instability of the neonate and use of HFOV. Also, various modes of non-invasive ventilation, such as nasal intermittent positive pressure ventilation (NIPPV) or nasal continuous positive airway pressure (nCPAP) that require wearing a cap on the head make it impossible to video EEG recording.[5,9,10]

In recent years, amplitude-integrated EEG (aEEG) has been used in daily clinical practice to detect electrographic seizures. Single-channel recording with electrodes placed in the biparietal region or bi-channel recording with electrodes placed in the centroparietal region have lower sensitivity and specificity in detecting seizures than cEEG, because the seizures may occur in other areas where EEG electrodes are not placed. The normal cEEG and aEEG findings changes with gestational age.[5,10] Patient had acute symptomatic seizures due to impairment of respiratory

function and impact hypoxia to immature brain. Video EEG recording had done after stabilization of respiratory function, when the neonate was on conventional mechanical ventilation. Interictal video EEG did not show epileptic discharges.

In the hospital the three most common used ASMs are phenobarbitone, midazolam and levetiracetam. We started phenobarbitone, as a first choice ASM, although it has been shown to stop seizures in about 50% of cases.[5,6,12] In accordance with the current recommendations, if neonatal seizures do not stop to phenobarbitone, levetiracetam or phenytoin may be used as a second choice ASM, as well as midazolam or lidocaine.[13,14] Because of side effects, such as hypotension, respiratory and CNS depression, midazolam is recommended in the treatment for refractory seizures and status epilepticus, especially in neonates requiring mechanical ventilation.[13,15,16]

Due to its favorable pharmacokinetics and safety profile, the use of levetiracetam in the treatment of neonatal seizures has increased significantly. The metabolism of levetiracetam does not take place in the liver, it has less interactions with other medications, as well as less side effects.[15,17] Also, its neuroprotective effect is highlighted.[18,19]

In neonatal seizures unresponsive to second-line ASM and with unknown seizure etiology, it is recommended that neonates receive pyridoxine, a form of vitamin B6, due to possible neonatal onset of pyridoxine-dependent epilepsy.[13]

A special challenge in the treatment of neonatal seizures that should not be forgotten is the immaturity of the liver and kidneys and changes in pharmacokinetics in neonates than older children and adult. There are variations in distribution, metabolism and excretion of ASMs, such as a slowed process of conjugation and other biochemical reactions in drug metabolism, slowed clearance, as well as a prolonged elimination half-life.[20-24]

CONCLUSION

Neonatal seizures are common in preterm neonates, especially in extremely preterm neonates, who are increasingly surviving due to advances in neonatal intensive therapy and care. Seizures in preterm neonates is associated with increased risk for poor neurodevelopmental outcome and epilepsy during childhood, so their early recognition and treatment is necessary. Nevertheless, phenobarbitone is still recommended as a first choice ASM, but it also emphasizes the importance of using midazolam and levetiracetam for the treatment of refractory neonatal seizures.

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