RECURRENT CONVULSIVE SYNDROME - CAUSES OF NEUROLOGICAL SEQUELAE

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Abstract

The seizures represent the most common clinical manifestation and distinct neurological disorder in newborns whit a frequency of 0.05% in newborns and 25% in preterm infants. The main causes of seizures are hypoxic-ischemic encephalopathy (EHI), intracranial hemorrhages and intracranial infections but there are some causes less common that make difficult to establish the etiology of the seizures. A 15 days old newborn baby girl was admitted whit dypnoea, subcostal and intercostals draft. During the hospitalization period she develop tonic-clonic seizures whit high frequency of the episodes in 24h, reaching from 2-3 episodes per day to 10-12/ 24h, changing their features, becoming generalized, with spasm in flexion (flexible arms and legs). Because of the small age of the patient and the complexity of the case makes it difficult to establish the etiology of the convulsive episodes been associated both metabolic and hypoxic-ischemic causes. Conclusions - during the neonatal period the etiology of the seizures is difficult to establish and most of the children develop multiple comorbidities such as tetraspastic, severe psychomotor retardation accompanied by eating disorders leading to deficiency anemia, protein-calorie malnutrition, rickets.

Key words: convulsive syndrome, seizures, new born

Introduction

The seizures represent the most common clinical manifestation and distinct neurological disorder in newborns. The frequency of seizures in the neonatal period is variable from 0.05% in newborns to 25% in premature infants (1,2). The incidence of seizures increases to 50% in cases of associated with seizures (3). The most common physical cause of the seizures is the hypoxic-ischemic encephalopathy (EHI) - 50-60% of cases; intracranial hemorrhages cause about 10% of neonatal convulsions. Intracranial infections causing 5-10% of neonatal seizures are most commonly nonbacterial. Other causes of neonatal seizures include genetic metabolic disorders (metabolic disorders of amino acids, urea cycle enzyme, abnormalities leucinosis, biotinidasis deficit, peroxisomal anomalies – Zellweger syndrome). Septicemia, and toxic metabolic abnormalities can also produce seizures in the neonatal period. (20)

Case report

The 15 days old newborn baby girl was admitted to the ICU Premature Children's ward at "Louis Turcanu"Emergency Hospital for dyspnoea, subcostal and intercostals draft, and distended abdomen volume. The physiological personal history shows that the infant comes from dispensarised evolving physiological pregnancy, naturally born at a gestational age of 38weeks, with 2900g birth weight, APGAR score 10/1' with good neonatal adaptation. Since the third day of life, overall condition worsens respiratory functional syndrome, fever (T =38 ° C) despite the antibiotic treatment.

On admission she presented an overall influenced general state, pale skin, heart rhythm disturbances CF180b/min, SaO2 94% and respiratory draft with RF 60 b/min, distended abdomen volume, generalized hypotonia. Laboratory data on admission revealed a mixed anemia, positive inflammatory markers (PCR=71.77mg/L, PCT=O,686 ng/ml) with positive blood cultures for Acinetobacter baumannii/haemolyticus at 72 hours.

On the second day of hospitalization appear the tonic-clonic seizures with decreased SaO2<50%, with peryoronasal cyanosis, spontaneously reversible. On the fifth day of hospitalization the patient shows a feverish spurt (T =38^{0}C) therefor CSF is harvested in order to rule out the meningitis suspicion. The inflammatory markers become negative under the antibiotic treatment. Convulsive episodes are maintained throughout the hospitalization lasting<1min, their frequency in 24h reaching from 2-3episodes per day to 10-12/ 24h, changing their features, becoming generalized, with spasm in flexion (flexible arms and legs), horizontal nystagmus, then look on the sunset, oculogyric.

To confirm the seizure etiology other biological investigations were made (table 1, 2). The cytogenetic report indicated karyotype 46, XX. Transfontanelar ultrasonography: minor bleeding of bilateral choroid plexus (Fig. 1).

Brain MRI and MRI angiography reveal normal appearance.

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It was established anticonvulsant therapy with Keppra syrup, initially 20mg/ kg/ day after reaching therapeutic dose of 40mg/ kg/day and Phenobarbital 10 mg/ kg/ day increasing the dose to 15mg/ kg/ day. The number of convulsive episodes intensifying it is decided to replace Phenobarbital with Phenytoin, initially in continue IV infusion thereafter administered orally. Evolution under anticonvulsant therapy was stationary, reducing convulsive episodes/ 24h, without their final cropping.

Alanie	***2.1mg/dL***	***Leucine***	***1 mg/dL***
Alphaaminobutyricacid	*0.1 mg/dL*	***Lyzine***	*1.3 mg/dL*
Arginine	*1 mg/dL*	***Mehtionine***	*0.3 mg/dL*
Asparagine	*0.7 mg/dL*	***Ornithine***	*0.6 mg/dL*
Aspartic acid	*0.3 mg/dL*	***Phenylalanine***	*0.7 mg/dL*
Carnosine	*<0.1 mg/dL*	***Phosphoethanolamine***	*<0.1 mg/dL*
Citruline	*0.2 mg/dL*	***Proline***	*1.8 mg/dL*
Cystine	***0.2 mg/dL ↓***	***Sarcosine***	*<0.1 mg/dL*
Glutamine	*6.1 mg/dL*	***Serine***	*1.5 mg/dL*
Glutamic acid	***3.3 mg/dL ↑***	***Taurine***	*0.7 mg/dL*
Glycine	*1.9 mg/dL*	***Tronina***	*0.9 mg/dL*
Histidine	*1 mg/dL*	***Tryptophan***	*1.1 mg/dL*
Hidroxiproline	*0.3 mg/dL*	***Tyrosine***	*1.2 mg/dL*
Izoleucine	*0.5 mg/dL*	***Valine***	*1.3 mg/dL*

Table 1. Plasma amino acids

CMV IgG	*>500 U/ml*	***ToxoIgG***	*187.6 UI/ml*
CMV IgM	*0.247*	***ToxoIgM***	*0.315 UI/ml*
Creatinkinaza		***325 U/L ↑***	
Orotic acid		*4 mg/g*	
Ammonia		***143.9 µmol/L↑***	
Na	137	138	
K	4.3	4.2	
Ca^{++}	1.1	1.2	
Ca total	2.39	2.49	
Mg	0.81	0.9	

Table 2. Biological investigations

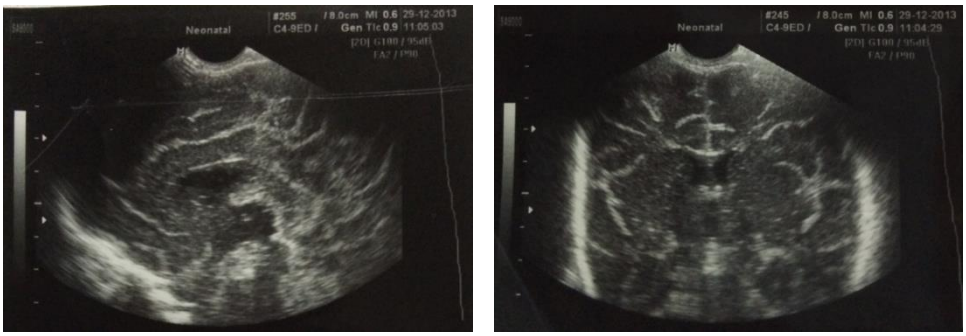

Fig.1: Transfontanelar ultrasound

Discussion

In recent years, significant advances in diagnosis and treatment in terms of neonatal seizures came into practice in neonatal intensive care.

The large majority of seizures in our population is due to perinatal asphyxia, known more correctly as hypoxic-ischemic encephalopathy, characterized by clinical evidence and laboratory investigations show acute or subacute cerebral abuse.(4) Asphyxia may be accompanied by hypoglycemia, hypocalcemia, hyponatremia due to antidiuretic hormone hypersecretion, especially in the first 3 days of life, and each of them individually can cause seizures. The onset seizures occure in the first 24 hours of life, being isolated at first and then become frequent and repetitive. Seizures shows various apperances: sharp, clonic seizures (focal and multifocal), tonic (focal and generalized), myoclonic (focal, multifocal and generalized).

Our infant showed no signs of hypoxia intra and postpartum, early neonatal adaptation is good. Transfontanelar ultrasonography reveals a choroid plexus hemorrhage, but no signs of cerebral ischemia.

Intracranial hemorrhage as only etiology is estimated at 10% of neonatal seizures, but the true incidence of it is not known because most newborns with intracranial hemorrhage show no clinical symptoms, including hemorrhages moderate to severe. (5) Symptomatic intracranial hemorrhage is much less frequent at the newborn at term - 4 per 10,000 live births. (6) The incidence is higher, however, if the fetal delivery is instrumental. (7) In 50% of cases bleeding occurs on the first day of life and 90% in the first four days. In the case of subarachnoid hemorrhage seizures occur more frequently in premature babies starts in the second day of life and between seizures newborn is in good general condition and 90% have a favorable prognosis. Seizures of intraventricular hemorrhage occur in premature babies in third day of life and tonic convulsions are associated with respiratory deterioration and death. Subdural hemorrhage determine onset seizures within 24 hours, associated trauma, usually with cerebral contusion. In this context they are focal seizures. Choroid plexus hemorrhage occurs in newborn at term, leading to complications with neurological sequelae in 15% of cases. (8)

Bacterial meningitis or viral encephalitis usually occur in sepsis, representing another common etiology of neonatal convulsions. The most common causes of nonbacterial infections include toxoplasmosis, CMV infection and less rubella. Escherichia coli bacterial pathogens common and Streptococcus pneumoniae. These causes should be excluded in any patient with seizures in the neonatal period, analyzing the TORCH complex and CSF. (9) The clinical and paraclinical background (fever, convulsions, positive inflammatory samples) raised the suspicion of infection of the central nervous system as a possible etiology of convulsion. Lumbar puncture was performed, and the TORCH serology refute the diagnosis of CNS infection.

Seizures can be caused by transient metabolic disorders including hypoglycemia, hypocalcemia and hypomagnesemia. Hyponatremia may be the result of inappropriate antidiuretic hormone secretion, due to trauma, infections and cerebral hypoxia being an unusual cause of neonatal convulsions. These metabolic disorders are often diagnosed early and treated quickly and effectively. The severity of neurological manifestations is directly correlated with the duration of the metabolic disorder.

Metabolic disorders are rarely among the causes of seizures in newborn babies, but should be considered if there is no evidence of hypoxic-ischemic injury, infection or bleeding.In many cases, etiological treatment is not available and the antiepileptics are used but unsuccessful. Seizures are rarely specific for a certain metabolic disorder likewise the EEG pattern.

Amino-acidopathy and organic acidaemia are the result of aminoacid and fatty acid metabolism dysfunction and can be manifested by seizures, movement disorders, cognitive and behavioral disorders.(10) Many of them produce epileptic encephalopathy. The seizure types and EEG pattern changes are variable, the myoclonic epilepsy being more common and the EEG shows slow wave dominated conduct. The most typical EEG changes in metabolic encephalopathies have the appearance of"burst supression" hyperarhytmia and generalized unloading wave/peak.

The Ohtahara syndrome also known as early infantile epileptic encephalopathy with the EEG pattern of "suppression-burst" type is characterized by onset of seizures since the first 10days of life, the most common being flexed tonic spasms lasting a few seconds. Some patients may experience partial seizures and myoclonic attacks. (11) The Ohtahara syndrome is determined by a variety of structural abnormalities of the CNS (developmental abnormalities, defective neuronal migration, microcephaly, hemimegalencefaly, hypoxic-ischemic encephalopathy), although metabolic disorders are also reported and include glycinic encephalopathy and abnormal mitochondria.(12) The EEG picture consists of a suppression-burst pattern with diffuse hot flashes peaks and ample sharp waves separated by periods of a few seconds of underactive EEG appearance. (13) They may present between 30 and 100 spasms per day. The prognosis is very severe with insufficient response to treatment.

In our case the convulsions started at 17 days of life, not exceeding 12 episodes/24 hours, the EEG pattern has changed, initially looking for "suppression-burst" after presenting an aspect of slow dysrhythmia causing wave extensive derivate tile from left of center. During pregnancy no echographyc aspects showing structural abnormalities of CNS were highlighted. The amount of glycine was normal. Symptoms improved under anticonvulsant therapy.

The prognosis varies depending on the underlying disease. A brain injury is proved that generally predicts a lower prognosis. EEG activity may serve as a prognostic marker, a normal activity correlates with a better prognosis. Seizures that occur within the first 3 days of life were associated with an increased risk of intraventricular hemorrhage, injury to the white matter of the brain and an increased death risk. (14) The risk of developing epilepsy after neonatal seizures varies in different studies, 2 % to 56%. Persistent seizures despite anticonvulsant therapy to children who had received two or more AEDs had an

unfavorable prognosis. 3 or 4 treatment failure AEDs, unlike two AEDs increase the risk of an unfavorable outcome. (15,16). Symptomatic neonatal seizures suggests a serious condition, the mortality rate is 15% in developed countries and up to 40 % in developing countries, and one third of survivors develop epilepsy. (17,18) Recurrent and prolonged neonatal convulsions may act on an epileptogenic substrate, causing further injuries, which are responsible for further clinical expression of epilepsy. (19)

Conclusions

The complexity of the case makes it difficult to establish the etiology of the convulsive episodes.

During the neonatal period, despite intensive therapy increasingly more specialized, the doctors treating seizures have difficulties in terms of prognosis and finding adequate solutions to therapeutic problems.

In our center, all children with a history of neonatal seizures are followed at least during the first year of life and are evaluated by a multidisciplinary team of experienced pediatric neurologists, developmental psychology specialists and physiotherapists.

The case was multidisciplinary evaluated, requiring repeated hospitalizations in the pediatric ward and infantile neuropsychiatry because of multiple associated complications, the patient reaching age 2 with multiple comorbidities: tetraspastic, severe psychomotor retardation accompanied by eating disorders leading to deficiency anemia, protein-calorie malnutrition, rickets. All these pathologies are associated with a severly unfavorable long-term prognosis

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