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ANTONOVICI FLORINA-MARINELA

PhD THESIS

SEIZURES MANAGEMENT IN THE NEONATAL PERIOD

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I. INTRODUCTION

The number of newborns at risk being discharged from the Neonatal Intensive Care Unit (NICU) is constantly growing due to improvements in intensive care techniques and experience in the field. Very high survival rates currently exist among newborns with previous life-threatening pathologies. However, despite progress in cardiopulmonary care and neonatal resuscitation techniques, newborns continue to suffer critical neurological complications. Up to a quarter of NICU patients are diagnosed with neonatal encephalopathy, brain injury, seizures and other significant neurological conditions. Neurological impairment of ischemic, hemorrhagic or infectious etiology and paroxysmal discharges are frequently associated with subsequent motor, cognitive, behavioural and sensory disorders.

Neonatal seizures are a major and ongoing challenge for clinicians due to discrete clinical signs, variable electro-clinical correlation, sometimes poor response to antiseizure drugs, and variable prognosis within wide limits from case to case depending on etiology. The diagnosis of neurological impairment in newborn should be made as early as possible through the use of screening tests or an effective clinical examination to identify individuals at risk of developing certain conditions.

The scientific purpose of this research is to investigate the newborns with neurological impairment such as neonatal seizures and hypoxic-ischemic encephalopathy, clinical, biological, electroencephalographic and imaging evaluation to establish prenatal and perinatal risk factors as well as long-term neurological possible predictors.

Neurological outcomes of newborns with neonatal seizures in relation to their etiology, gestational age, aEEG (amplitude-integrated electroencephalography) background pattern or age at seizure onset has been also researched.

Another important objective of the research was establishing correlation between the aEEG background patterns of critically ill patients from NICU and the

degree of clinical impairment and biological parameters of hypoxic-ischemic encephalopathy. Patients with moderate or severe perinatal hypoxic-ischemic encephalopathy, who often develop subclinical, only-electroencephalographic seizures, may thus benefit from early treatment, with favourable outcome on subsequent neurological development.

II. GENERAL PART

Neonatal seizures, one of the most common neurological pathologies in the neonatal period, reflect a variety of pre-, peri-, and postnatal disorders of the central nervous system and they are more common in the neonatal period than in other ages. Also, some newborns in NICU are at risk for neurological sequelae due to immaturity or certain diseases. The reported prevalence and incidence of neonatal seizures vary considerable, both due to differences in the methodology of the studies, especially in the way of identifying neonatal seizures, but also due to the geographical position and the degree of development of the countries, gestational age and birth weight.

Determining the etiology of seizures is critical because it provides the opportunity to initiate specific treatment and provides important prognostic information. Although there are many causes of neonatal seizures, a relatively limited set of aetiologies is critical for most affected newborn. Of these, perinatal hypoxic-ischemic encephalopathy (HIE) is the most common cause of seizures in both full-term and preterm newborns, accounting for nearly half of all determinants.

EEG monitoring is particularly important in NICU, providing important diagnostic and prognostic information. A valuable and increasingly used method for the continuous monitoring of brain electrical activity in critically ill newborns in NICU is amplitude-integrated electroencephalography. aEEG monitoring is performed at the bedside and uses a small number of electrodes, which are maintained for at least 24 hours.

According to current guidelines, conventional EEG monitoring is considered the gold standard, provides a reliable diagnosis of neonatal seizures, and seizures discharged on aEEG provide the probability of diagnosis. aEEG recordings are evaluated mainly for background pattern and seizure activity detection. The background information may be useful in determining the degree of encephalopathy, the effect of antiepileptic drug medication and the long-term prognosis.

III. SPECIAL PART

We conducted 2 studies involving term and preterm newborns admitted to the NICU and aEEG monitored for the diagnosis of neonatal seizures – in the first study, and neurological impairment secondary to hypoxic-ischemic encephalopathy, with or without clinical seizures - the second study. These were prospective studies performed in Neonatology and Preterm Department of "Louis Turcanu" Children's Emergency Clinical Hospital Timisoara over a period of 3 years. The patients were clinically and electroencephalographically assessed and in terms of certain biological and paraclinical important features of the seizures or neurological impairments. Their long-term outcome was subsequently followed around the age of 18 months.

III.1. The first study: Monitoring and assessment of patients with neonatal seizures and long-term neurological outcomes.

In this first study we aimed to monitor newborns with neonatal seizures, to evaluate them clinically, electroencephalographically and brain imaging, to follow the risk factors and the etiological factors of the seizures and to identify possible predictors of neurological outcome in these patients. Newborn monitoring in neonatal intensive care units (NICU) is mandatory, but neurological and especially electroencephalographic (EEG) monitoring can be overlooked or delayed until the newborn is clinically stable. However, the neonatal period is associated with the highest risk of seizures in humans, and the clinical symptoms may often be discrete, but the

evolution and long-term neurodevelopmental disorders in these patients may be important. In response to this issue, we conducted a study to evaluate newborns who experienced neonatal seizures in the NICU and monitored their long-term neurological development.

The criteria for inclusion in the study in the neonatal period were as follows: term newborns up to 28 days old with clinical diagnosis or clinical suspicion of neonatal seizures; preterm newborns whose corrected GA has not exceeded 44 weeks at the onset of seizures, with clinical diagnosis or clinical suspicion of neonatal seizures; aEEG monitoring for at least 24 h, instituted prior to the time of starting antiepileptic drug treatment.

Seizure events were classified according to the Neonatal Seizures Task Force 2020 Classification: clonic, tonic, myoclonic, autonomic/automatisms, epileptic spasms.

aEEG background pattern was assessed. The background pattern from the beginning of aEEG recording and the pattern observed in evolution at 24 h of monitoring was noted. The aEEG background pattern was interpreted as follows:

a) *Normal/near-normal background activity*: CNV - Continuous Normal Voltage, or DNV - Discontinuous Normal Voltage;
b) *Abnormal pattern*: BS - "Burst Suppression", CLV - Continuous Low Voltage, or FT - Inactive, Flat Trace.
c) *Seizures/epileptic activity*: Sz – Seizures, or SE - Status epilepticus.

Sleep-wake cycle (SWC) presence on aEEG was checked. We considered:

a) *No SWC*: no sinusoidal variations of the aEEG background;

b) *Developed SWC*: clearly identifiable sinusoidal changes with cycle duration ≥20 min.

Regarding the **long-term outcome** of patients, unfavorable/poor outcome was considered in patients with epilepsy, cerebral palsy, severe psychomotor delay, or those who were deceased by around 12–18 months of age. The patients with favorable/good outcome were those for whom the above diagnoses were not mentioned at post-discharge assessments in the hospital.

Results and discussions

The study group consisted of 73 patients, 36 (49.31%) term newborns and 37 (50.68%) preterm newborns. Gestational age (GA) ranged from 22 to 42 weeks and birth weight (BW) was between 450g and 4500g. The most common cause of neonatal seizures in the present study was HIE (49%), without significant differences in terms of gestational age. Correlation between clinical seizure type and aEEG background pattern trace was performed and highly statistically significant differences were observed. Infants with epileptic spasms had a good correlation with aEEG pattern and those with tonic seizures also showed seizure or epileptic pattern in high percentage (87.5%). Newborns with clonic seizures showed 56.5% electroencephalographic correlation. Thus, 43.5% of them presented seizures in a normal or quasi-normal pattern, and 13% had status epilepticus pattern. Autonomic seizures correlated with aEEG in 57.7% and myoclonic seizures only in 25% of cases.

We analysed the long-term evolution of patients according to: the electroencephalographic background pattern observed during aEEG monitoring, the presence/absence of SWC, Apgar score, GA, gender. Following the computerized search of medical records in the medical unit's online database, of the 73 patients evaluated for neonatal seizures in the neonatal period, only 59 remained in the study. In terms of long-term outcomes, the data showed statistically significant differences in all categories followed: sleep-wake cycle, aEEG background pattern at the beginning of monitoring and aEEG trace at 24 hours of monitoring, after initiation of antiepileptic drug (AED) therapy. A higher Apgar score is associated with better neurological outcome in children with neonatal seizures. aEEG background pattern is a strong predictor of unfavorable

neurological outcomes. Birth-related parameters such as the Apgar score, need for resuscitation at birth and birth weight all showed statistically significant differences between the outcome groups. The age at seizure onset appears to be a significant prognostic factor. Meanwhile, gender did not show a significant association with outcome, and gestational age showed a borderline association. The presence or absence of SWC on aEEG did not correlate with the long-term neurological outcome of patients. When comparing seizure etiology and long-term outcome of patients, the most common cause of the neurological condition in both outcome groups was HIE, accounting for 50.0% of the unfavorable outcomes and 48.0% of the favorable outcomes. This suggests that HIE is a significant factor in the neurological evolution of patients, regardless of the outcome. We also found a statistically significant association between preterm birth and unfavorable neurological outcomes.

III.2. The second study: Assessment of newborns at neurological risk in Neonatal Intensive Care Unit

The second study aimed to assess clinically, biologically and electroencephalographically newborns with HIE following perinatal asphyxia in the NICU, known the high incidence of electrographic-only seizures and known that the severity of the disease reflects the medium- and long-term outcome of the patients.

The inclusion criteria for the study were: gestational age ≥36 weeks, history of perinatal asphyxia, Sarnat criteria of mild/moderate/severe HIE, aEEG performed within the first 72 hours of life, age at admission </= 48 hours of life.

Laboratory common tests were processed in our hospital laboratory upon admission to NICU: serum glucose, serum creatinine, creatine kinase (CK) and lactate dehydrogenase (LDH), nonspecific markers of kidney and brain damage secondary to perinatal hypoxia.

Results and discussions

Forty-three newborns with HIE were enrolled in the study. Of these, 15 (34.9%) had mild HIE, 21 (48.8%) moderate HIE and 7 (16.2%) had severe HIE, according to the modified clinical Sarnat score. Clinical seizures were associated with perinatal hypoxia in a significantly increased percentage in the moderate HIE group. 20% of patients with mild HIE developed clinically observed neonatal seizures in the first days of life, and in 13.3% of these, aEEG records confirmed the seizures. In contrast, 71.4% of newborns with severe HIE had seizures or status epilepticus during aEEG monitoring, although only 42.8% had clinical manifestations. Also, 28.5% of newborns with severe HIE had "burst suppression" pattern. In the group of newborns with moderate HIE, seizure manifestations were entirely in the aEEG trace. Admission hypoglycemia was present in most newborns. Creatinine, CK and LDH had elevated mean values in the neonates with severe HIE, both at admission and in the 3rd day of life. In patients with moderate HIE, only LDH and CK were elevated, and newborns with mild HIE showed slightly elevated CK. Statistically significant differences between the 3 groups of our study were noted in terms of creatinine and CK at admission and LDH in the 3rd day of life.

FINAL CONCLUSIONS

Our study highlights the importance of early EEG monitoring in the NICU and provides valuable insights into predictors of unfavorable neurological outcomes in newborns who experienced neonatal seizures.

Our findings indicate that abnormal aEEG background pattern and a low Apgar score are strong predictors of unfavorable neurological outcomes in children with neonatal seizures. Patients with an abnormal aEEG background pattern in dynamics (BS, CLV, FT) are more likely to have an unfavorable neurological outcome compared to newborns with normal aEEG results. In contrast, SWC in aEEG did not prove to be a long-term prognostic factor in our study, although statistically significant differences were observed between patients with favorable versus unfavorable outcomes regarding SWC.

Furthermore, we found a direct correlation between preterm birth and unfavorable neurological outcomes.

Birth-related parameters such as a low Apgar score, need for resuscitation at birth and low BW have been shown to be negative prognostic factors at distance. Age at seizure onset also appears to be a significant prognostic factor, with the majority of patients in the poor outcome group having seizures after the first week of life.

Regarding the seizure etiology and long-term outcomes, HIE was the most common cause in both good/poor outcome groups.

Common blood tests in association with aEEG monitoring and rigorous neurological assessment can predict short term outcome in patient with HIE and can help clinicians predict even long-term outcomes in severe neurological impairment.

The current research opens new perspectives for research into assessment of newborns at neurological risk, early diagnosis, implementation of standards and protocols for investigations to improve the long-term prognosis of these patients.