Early - life seizures: alarm bell for often severe clinical outcome

Early life seizures (ELS) are a not uncommon clinical manifestations in infancy affecting from 1.8 to 3.5/1000 live birth. In infancy with rare exception of seizures typically benign which include the Benign Familiar Neonatal Epilepsy (BFNE), Febrile Seizures simplex (FSs) and Acute Symptomatic Seizures (ASS), ELS are clinical expression of a series of severe disorders classified as ”Early-Onset Epileptic Encephalopathies (EOEE). These are an heterogeneous group of disorders in which epileptic activity itself (ictal or interictal) impairs cognitive and behavioural function above and beyond what is expected from the underlying pathology alone.

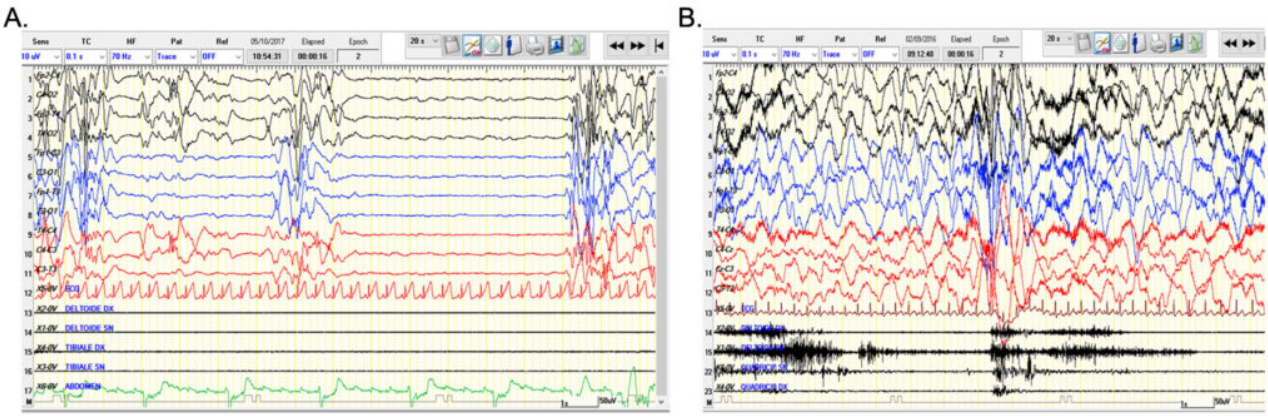


Fig. 1. A. EEG during sleep showing Burst-suppression pattern in 3 months infant with Ohtahara syndrome.
B. EEG during sleep showing hypsarrhythmia pattern in a 5 months infant with West syndrome.

Etiology

The brain intrauterine and early life periods are critical in the brain development since the synaptogenesis is in phase of evolution and abnormal events may interfere causing severe brain damage. ELS are mainly symptomatic, the most frequent being the hypoxic-ischemic encephalopathy (HIE). Numes et al distinguished the etiological events in ELS in 7 groups: (a) HIE; (b) cortical malformations; (c) central nervous system (CNS) infections; (d) metabolic (electrolyte imbalance, inborn errors of metabolism, vitamin-related disorders and withdrawal seizures); (e) genetic (channelopathies, chromosomal disorder, other gene disorders; (f) vascular (stroke and hemorrhage) and (g) unknown. Overlapping events of some of the causes are frequently found.
According to recent acquisitions more than 265 genes have been linked to epileptic disorders and some of these including STXBPI, ARX, AARS, ADSL, ALDH7A1, ARHGEF9, BRAT1, SLC25A22, KCNQ2, CDKL5, SCN1A, and PCDH19, CACNA1A, CACA2D2, CASK, CHD2, CLCN4, DNM1, DOCK7, EEF1A2, FOXG1, GABRA1, GABRB1, GABRD3, GABRG2 have been recognized to be

associated with EOEE.

Clinical focus

> Neonatal seizures are distinguished on the basis of the semiology in clonic, tonic, myoclonic, autonomic, spasms, segmental and autonomic.
> Early-Onset Epileptic Encephalophaties include:

Early Infantile Epileptic Encephalopathy (EIEE) also known as Ohtahara syndrome. It is clinically characterized by early onset seizures presenting in 1/3 of cases in the neonatal period by paroxysmal jerk, followed by sustained tonic extensor posturing of the upper and /or lower extremities lasting several seconds, and appearing in cluster. Interictal EEG is characterized by high voltage burst of slow waves mixed with multifocal spikes with phases of flat suppression.

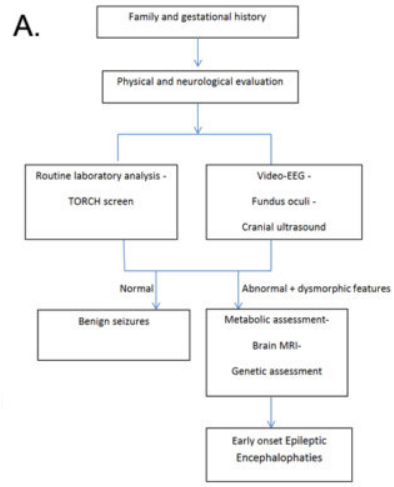
Early myoclonic encephalopathy the affected infant manifested with myoclonus as the main seizures type with frequent episodes of erratic partial seizures. Focal myoclonic are localized in the face or extremities with migration from a part of body to another.

Epilepsy of infancy with migrating focal seizures. The disorder manifest with polymorphous focal seizures involving part of the body sometimes in alternating sides. Interictal EEG showing multifocal independent epileptic discharges, prominent slowing and disorganization.

West syndrome is defined by the classic triad of infantile spasms, hypsarrhythmia and developmental arrest or regression. The seizures occur in cluster and may manifest in flexion, in extension or mixed.

Laboratory investigations (Tab. 1A)
Family and gestational history, detailed clinical examination, fundus examination, blood glucose, NO2, electrolytes, plasma and urine amino-acids, thyroid function, lactate, blood ammonia levels, organic acids, TORCH screen. ECG, video-EEG awake and during sleep (Fig. 1A and 1B). Cranial ultrasound, Brain MRI and molecular investigations. We have found a clear correlation of dysmorphism in association to epileptic seizures in all the cases of anomalies of molecular origin.

A.



B.

Early onset epilepsy	Treatment
Pyridoxine dependent epilepsy	Pyridoxine 100 mg or 30mg/kg
Pyridoxal-5-phosphate dependent epilepsy	Pyridoxal-5-phosphate 30mg/kg
SCN2A-related epileptic encephalopathy	High dose phenytoin
SCN8A-related epileptic encephalopathy	High dose phenytoin
West syndrome	ACTH i.m. 3-4 UI/Kg/day
Dravet syndrome	Lamotrigine and phenytoin
Familial epilepsy syndromes with potassium channel mutations	Carbamazepine
Epilepsy of infancy with migrating focal seizures	Quinidine
Benign familial infantile seizures	Carbamazepine
GLUT1 deficiency syndrome	Ketogenic diet
Tuberous sclerosis complex	Vigabatrin 50-100mg/kg/day Consider everolimus

Tab. 1 A. Clinical assessment in infant with early onset seizures.
B. Treatment usually recommended in some cases of EOEE.

Treatment

Treatment of infants with EOEE is quite challenging with most of the several antiepileptic drugs showing modest efficacy. The identification of genetic mutation is important for the modern use of targhet treatment. Treatment usually recommended in cases of EOEE is reported in Table 1B.

Outcome

In a survey of outcome of children with EOEE the mean (SD) age of death was 12,9 +- 14,1 months, most infant (58,8%) survived less than one year. The main causes were pneumoniae/respiratory illness or sudden unexpected death in epilepsy (SUDEP).

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