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"A RARE CASE OF EARLY INFANTILE EPILEPTIC ENCEPHALOPATHY"

Neurology

Dr. K. Joy Mounica Post Graduate in Neurology, GMC, Guntur
Dr. N. Hemanth Kumar Post Graduate in Neurology, GMC, Guntur
Dr. NV Sundarachary MD, DM, Prof & HOD Neurology, GMC, Guntur

ABSTRACT

Early infantile epileptic encephalopathy (EIEE), also known as Ohtahara syndrome, is characterized by intractable tonic seizures in the setting of a severe encephalopathy and a burst-suppression background pattern on EEG. Incidence has been estimated at 1/100 000 births in Japan and 1/50,000 births in the U.K. Approximately 100 cases total have been reported but this may be an underestimate. Ohtahara syndrome is a rare clinico-EEG syndrome. Gold standard investigation is genetic panel for epilepsy in case of nil structural abnormalities. It is refractory to any mode of treatment including ketogenic diet and surgery and carries highest mortality rate, die in infancy.

KEYWORDS

Background:
Early infantile epileptic encephalopathy (EIEE), also known as Ohtahara syndrome, is characterized by intractable *tonic* seizures in the setting of a severe encephalopathy and a burst-suppression background pattern on EEG. Many infants with EIEE harbor overt cerebral dysgenesis or cortical dysplasias. Survivors often develop typical infantile spasms with hypsarrhythmia and Lennox–Gastaut syndrome accompanied by multifocal spikes on the electroencephalogram.

Case Report:
A 14 mon old male child born of non-consanguineous parentage, product of IVF procedure, full term gestation delivered through elective LSCS, first in birth order with no history of birth asphyxia with global developmental delay with multiple episodes of non-febrile refractory epileptic spasms since first week (second day) of birth was on polytherapy (Anti-Epileptic drugs) with no neurocutaneous markers with brisk tendon reflexes and bilateral extensor response of plantars with no developmental defects, no CNS infection, no motor or cerebellar involvement. Routine biochemical tests including serum calcium, serum magnesium and serum blood sugars are normal. EEG (both sleep and wakeful state) recorded on 5th day of birth revealed 1-2 seconds of sharp waves and sharply contoured slow waves followed by voltage attenuation periods lasting for 5-10 seconds (Burst suppression pattern)Figure-1. Newborn screening test for Fatty acid oxidation disorders, organic aciduria and amino aciduria was done and are ruled out. Routine CSF analysis was normal including CSF glycine (6.4nmol/ml) levels. EEG's recorded at end of first, third and fifth month was consistent with burst-suppression pattern and disorganised background. In seventh month EEG recorded revealed burst-suppression pattern with marked asymmetry and asynchronyFigure-2 (Left> Right).MR imaging of brain was normal, while PET-CT brain revealed decreased tracer uptake over left half of cerebral cortexFigure-3 which was not correlating with EEG findings. Hence sent for Genetic panel testing which revealed KCNQ2 mutationsFigure-4.Child was put on polytherapy with levetiracetam, phenobarbital and vigabatrin. During this period, no changes were observed in seizure frequency but EEG revealed hysarrhythmia.

DISCUSSION:
Etiologies are heterogenous, which include malformations of brain development (Hemimegalencephaly, Porencephaly, Cerebral dysgenesis etc), Metabolic disorders like glycine encephalopathy and Genetic mutations like ARX (Aristaless-related homeobox protein), CDKL5 (Cyclin-dependent kinase like 5 protein involved in regulation of MeCP2), SLC25A22 (mitochondrial glutamate carrier), STXBP1 (syntaxin binding protein 1),KCNQ2 mutations, SCN2A (alpha subunit of sodium channel).[1]

Ohtahara syndrome has male preponderance and is characterized by Tonic spasms within first 10days of life which often consist of tonic forward flexion that lasts 1 to 10 seconds often occurring in clusters 10 to 300 times per day. The spasms may be lateralized and may occur during wakefulness and sleep. Soon after the onset of the seizures, the infant becomes hypotonic with poor activity, and psychomotor development is arrested with subsequent development of diplegia, spasticity, ataxia, or dystonia.

The EEG picture often shows a characteristic burst-suppression pattern.[1]

- The EEG background consists of high voltage (150 to 350 microvolt) slow waves with intermixed multifocal spikes lasting 2 to 3 seconds with periods of suppression lasting for 3 to 5 seconds and this pattern of burst suppression is continuous during wakefulness and sleep.
- The burst-suppression pattern disappears within the first 6 months of life and is often replaced by hypsarrhythmia with progression to West syndrome; it may later progress to a slow-spike wave EEG pattern with Lennox-Gastaut syndrome.

Brain imaging often confirms the presence of an underlying cerebral malformation. Metabolic screening to rule out metabolic disorders and Genetic testing to detect underlying mutation.

We added vigabatrin[3] to phenobarbital therapy as Seizures in a Ohtahara syndrome failed to respond to conventional anticonvulsants but were controlled with vigabatrin monotherapy.

Ohtahara syndrome carries high mortality and morbidity. About half of the patients die in infancy and others develop permanent severe mental and neurologic deficits. Often, patients who survive may progress into West syndrome and later into Lennox-Gastaut syndrome with persistent high mortality and severe psychomotor delays.[2]

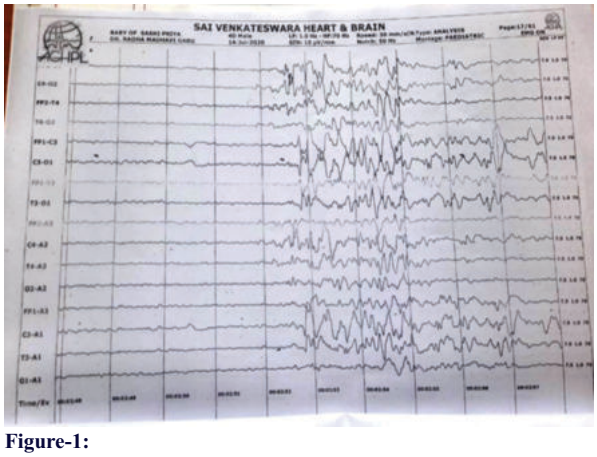

Figure-1:

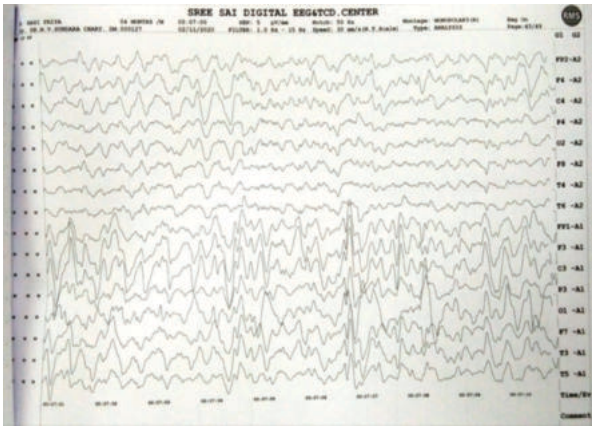

Figure-2:

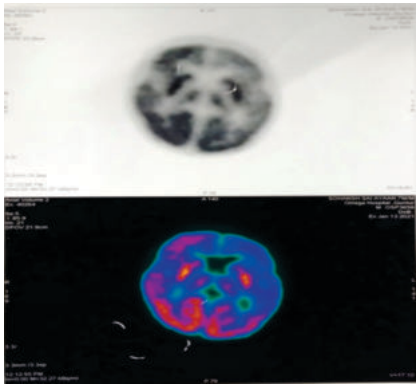

Figure-3:

CLINICAL DIAGNOSIS / SYMPTOMS / HISTORY

Baby *K. Sohansh Sai Ayaan*, born of a non-consanguineous marriage, presented with clinical indications of global developmental delay, respiratory distress at birth, hyperbilirubinemia on day 5, recurrent refractory seizures, right focal onset seizures with impaired awareness, brisk deep tendon reflexes, partial neck holding, no rollover, fisting of hands, ankle clonus, pyramidal signs, spasticity (upper limb > lower limb). His brain MRI at 4 months of age showed progressive thinning of the corpus callosum and prominent subarachnoid spaces. PET-CT Scan showed decreased tracer uptake in the left half of the cerebral cortex, left thalamus and increased uptake in the left medial temporal lobe. EEG at day 24, 2 months and 4 months of age were abnormal. He is suspected to be affected with neonatal onset epilepsy and has been evaluated for pathogenic variations.

RESULTS

LIKELY PATHOGENIC VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Gene (Transcript) *	Location	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
KCNQ2 (-) (ENST00000359125.6)	Exon 4	c.560C>T **(p.Ser187Phe)**	Heterozygous	Developmental and epileptic encephalopathy-7 / Benign familial neonatal seizures-1	Autosomal dominant	Likely Pathogenic

Parental testing is strongly recommended, and classification of the variant(s) may change based on segregation

Figure-4:

REFERENCES:

1. Swaiman's Pediatric Neurology Principles and Practice sixth edition chap 70 pg 554
2. Swaiman's Pediatric Neurology Principles and Practice sixth edition chap 70 pg 555
3. Baxter PS, Gardner-Medvin D, Barwick DD, Ince P, Livingston J, Murdoch-Eaton D. Vigabatrin monotherapy in resistant neonatal seizures. Seizure 1995;4:57-9.