

CDKL5 Encephalopathy: A Rare Cause of Infantile Epileptic Encephalopathy

'Epileptic encephalopathy' is defined as an epilepsy syndrome where the seizures and/or interictal EEG discharge have permanent deleterious effects on brain development [1]. Most of them present with seizures that are refractory to treatment, and have a poor prognosis. The etiology is very diverse and most of them are due to a genetic or metabolic cause. While the metabolic causes for refractory epilepsy in infancy (*e.g.* pyridoxine dependency, non-ketotic hyperglycinemia) are commonly thought of and investigated for, many pediatricians may not be well versed with the genetic causes of epileptic encephalopathy.

Recently many genes have been found to be associated with early onset epileptic encephalopathy [2]. A correct diagnosis helps in counseling of parents, avoiding unnecessary treatment with antiepileptic drugs, hormones and vitamins, and enabling prenatal diagnosis.

Mutations within the X-linked Cyclin-dependent kinase-like 5 (*CDKL5*) gene are one of the important causes of early-onset epileptic encephalopathies [2]. Patients present with refractory epilepsy, beginning before the age of three months, often in neonatal period, with very frequent seizures and severe developmental delay or regression. We herein report a girl with *CDKL5* encephalopathy where the diagnosis was delayed by almost 18 months. She had seizures (clonic seizures and spasms, 5-15 episodes per day) starting at age of 1 month with significant developmental delay. There was severe microcephaly (head circumference 40 cm), hypotonia and poor eye contact. Biochemical tests including tests, for neurometabolic disorders (tandem mass spectrometry, lactate, ammonia, urine gas chromatography/mass spectrometry) were all within normal limits. Cerebrospinal fluid (CSF) analysis was normal with normal sugar, lactate, pipelicolic acid and glycine levels. Magnetic resonance imaging (MRI) of brain was normal (done twice at 12 months interval). While the first EEG was normal, subsequent EEGs showed multifocal epilepsy with burst suppression pattern both during sleep and while awake. She did not respond to multiple antiepileptic drugs (newer and conventional in combination), trial of pyridoxine, folinic acid, pyridoxal phosphate and ketogenic diet.

Finally, genetic study for infantile epileptic encephalopathy panel (next generation sequencing) was done and a novel heterozygous missense mutation in *CDKL5* gene (chrX: 18598083; A>A/G) which causes an amino acid change in codon 133, exon 7 [c.398A>A/G (ENST00000379989); p.H133R] was detected. This mutation was also found to be damaging by SIFT, PolyPhen, likelihood ratio test and Mutation Taster.

CDKL5 encephalopathy is rare disorder causing refractory epilepsy and Rett's syndrome like phenotype. It is characterized by refractory epilepsy in girls, severe hypotonia, with severe psychomotor delay and features that overlap with Rett syndrome. There are three clinical stages of epilepsy in patients with *CDKL5* mutations: (i) early-onset, recurrent convulsive seizures, severe hypotonia, and normal findings of interictal electroencephalograms; (ii) epileptic encephalopathy with infantile spasms and hypsarrhythmia; and (iii) refractory tonic or myoclonic epilepsy with EEG showing multifocal epilepsy [3-5]. Treatment is only supportive and symptomatic.

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