Epileptic encephalopathy, visual impairment and developmental retardation: CDKL5 deficiency disorder

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OBJECTIVES

The cyclin-dependent kinase like 5 (CDKL5) deficiency is a rare neurologic condition characterized by early onset developmental delay and epileptic encephalopathy. We aimed to description of seizure types in patients with CDKL5 deficiency, an assessment of the seizure frequency, cortical visual impairment, and developmental milestones.

METHODS

Seven patients with diagnosed with CDKL5 deficiency were compared clinical and EEG findings, seizures' response to treatment and prognosis.

RESULTS

The median age was 17.2±11.3 months. Mean age of seizure onset was 2.5±1.6 months. The demographic and clinical data, brain MRI and EEG features, and prognosis of patients are summarised in Table 1. All of them had psychomotor retardation. Visual impairment was present in one of patient, and was the first symptom before seizures. EEG of the patient with visual impairment revealed epileptic activities in the posterior regions of both hemispheres. Genetic analysis revealed different CDKL5 mutations for each patient. Patients was received steroid and multiple antiepileptic treatment. Also, two patients received ketogenic diet. Average follow-up time was 17.7±7,5 months. Seizures remained resistant to treatment, and continued daily, but a significant reduction in seizures was observed in two patients with the ketogenic diet.

REFERENCES

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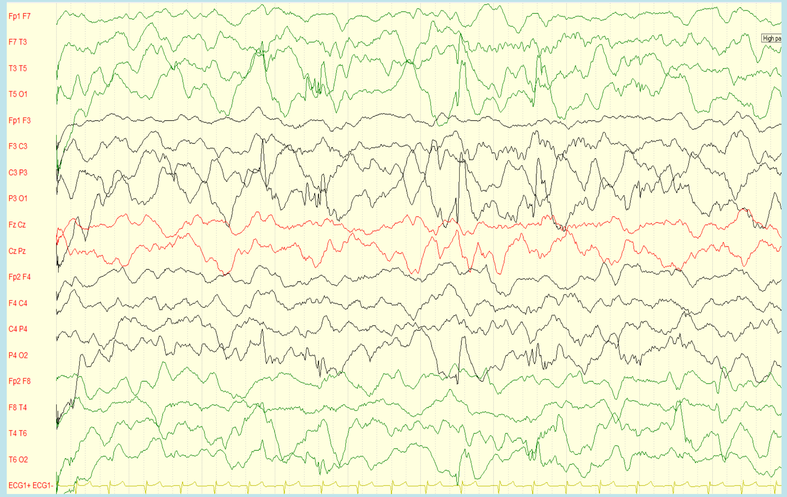

Figure 1. EEG of a 6-month-old girl with CDKL5 mutation who had visual impairment showed bilateral diffuse spikes in the occipital region.

CONCULSIONS

CDKL5 gene encodes a serine-threonine kinase that is highly expressed in the developing brain. It is pointed out that loss of function of CDKL5 underlies CDKL5 Deficiency Disorder, an X-linked predominant disease characterized by early-onset epileptic encephalopathy and developmental delay, which generally affects girls more than boys. The type and position of CDKL5 variants with different effects on the protein have been reported to affect clinical presentation. Genotype-phenotype correlations are still challenging. Although most seizure type are epileptic spasm, all types of seizures can be seen. Visual impairment should be the first sign of CDKL5 deficiency. Clinical severity may be related to the location and type of mutations. Therefore, further research is needed to investigate the genotype-phenotype correlation of CDKL5 mutations. The ketogenic diet is also a good alternative for seizure control in this group of epilepsy.

Table 1. Demographic information, clinical, brain MRI, and EEG features and prognosis of patients with a CDKL5 mutation

Case No	Sex	Age	Age of seizure onset	Consanguinity	Clinic features at presentation	Brain MRI	EEG	Genetic analysis	Treatment	Neurologic outcome
1	F	11 months	5 m	No	Visual impairment, generalized tonic, and myoclonic seizures, hypotonicity, hyperreactive deep tendon reflexes	Normal	İrregular background rhythm, and epileptic activity at both occipital regions	CDKL5 gene (c.2222C>G) heterozygote variant	Levetiracetam, valproic acid, clobazam, ketogenic diet, cannabidiol	Short-term seizures continue, increase in social development
2	F	36 months	2 m	No	Epileptic spasm, can sit with assistance, not walking. Uses 20-30 words, no sentences	Normal	İrregular background rhythm, multifocal and generalized epileptic activity	CDKL5 gene p.E21K (c.61G>A) heterozygote variant	Vigabatrin, Adrenocorticotropic hormone (ACTH), ketogenic diet	Seizures continue, she started to say words
3	M	30 months	2 m	No	Generalized tonic, and myoclonic seizures, can sit with assistance, no walking, no talking	Mild cerebral atrophy, and enlargement of ventricles due to central atrophy	İrregular background rhythm, multifocal and generalized epileptic activity	CDKL5 gene p.R735fs (c.2205_2206del) hemizygous variant	Vigabatrin, clobazam, valproic acid, ACTH	Seizures continue
4	F	10 months	1 m	Yes	Generalized clonic seizures, hypotonic, hyperreactive deep tendon reflexes	Normal	İrregular background rhythm, multifocal and generalized epileptic activity	CDKL5 gene c.554+4A>G heterozygote variant	Levetiracetam, valproic acid, clobazam, lamotrigine	Reduction in seizures
5	F	70 months	5 m	No	Epileptic spasm,and generalized tonic hypotonic, walks unsteadily	Normal	İrregular background rhythm, multifocal and generalized epileptic activity	CDKL5 gene c.282+3A>T heterozygote	Phenobarbital, vigabatrin, valproic acid, topiramate	Reduction in seizures
6	F	12 months	1 m	No	Generalized clonic seizures, no object tracking hypotonic, no walking	Normal	İrregular background rhythm, and epileptic activity at both occipital regions	CDKL5 gene p.L220P; c.659T>C)	Levetiracetam, clobazam, lamotrigine, ketogenic diet	Significant decrease in seizures, increase in social development
7	F	18 months	3 m	No	Focal clonic	Normal	Normal background rhythm, and temporal spikes	CDKL5 gene p.(His844Thrfs*66 heterozygote	Levetiracetam	Seizures continue