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Epileptic Disorders

CLINICAL VIGNETTE

Mosaic *CLTC* pathogenic variant causing focal epilepsy with normal intelligence

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CLTC (OMIM 118955) encodes clathrin heavy chain 1 (CLTC), a protein involved in the generation of envelopes that cover the cytoplasmic face of clathrin-covered intracellular organelles, in intracellular trafficking of receptors and endocytosis of many macromolecules, and in the stabilization of kinetochore fibers in the mitotic spindle.[1–3] CLTC is widely expressed in the brain and plays a role in neuronal transmission by facilitating the recycling and release of vesicles at the presynaptic termini of neurons.[4] Heterozygous *CLTC* pathogenic variants cause global developmental impairment, often accompanied by dysmorphic features, microcephaly, hypotonia, or ataxia.[5–7] Structural brain abnormalities occur in 80% of individuals, the most common being corpus callosum hypoplasia.[6] Seizures are reported in 38%, with both generalized and focal semiologies described; age of onset ranges from the neonatal period to adulthood, and seizures are usually pharmacoresponsive.[6] In this paper, we report the first patient with a mosaic *CLTC* pathogenic variant, in whom several unique clinical features were observed.

A 6-year-old girl, previously well and with normal developmental milestones, had a 2-week history of episodes of sudden fear and increased heart rate. With a typical event, she would run to a parent, saying she was frightened because monsters or thieves were trying to hurt her. Her heart rate was elevated during the events, and she sometimes had whole-body hyperkinetic movements. Duration of the events was usually 30 s and there was no apparent alteration in awareness. The events occurred from wakefulness or sleep, and frequency progressively increased to the point at which they occurred every 20–30 min.

The patient was initially referred to cardiology; after heart function was found to be normal, the neurology service was consulted. Continuous video EEG monitoring was initiated and 28 seizures were recorded during the first 17 h, despite carbamazepine and levetiracetam being initiated. Clinically, she had ictal hyperkinetic movements and tachycardia up to 200 beats/min. The interictal EEG showed abundant focal spikes, sharp waves, and spike–wave discharges over the frontal regions. During seizures, an evolving ictal rhythm was seen over the frontal regions, without clear laterality (Figure 1). Seizures were initially pharmacoresistant, and she received intravenous doses of midazolam, phenytoin, and phenobarbital. She eventually came under good control on combination therapy of valproic acid and clobazam.

From a developmental perspective, she walked and spoke her first word at 12 months. Motor and language milestones were all normal, though she was subsequently diagnosed with attention deficit disorder. She is of Lebanese background with no known consanguinity and no known family history of epilepsy, intellectual development disorder, or other neurological disorders.

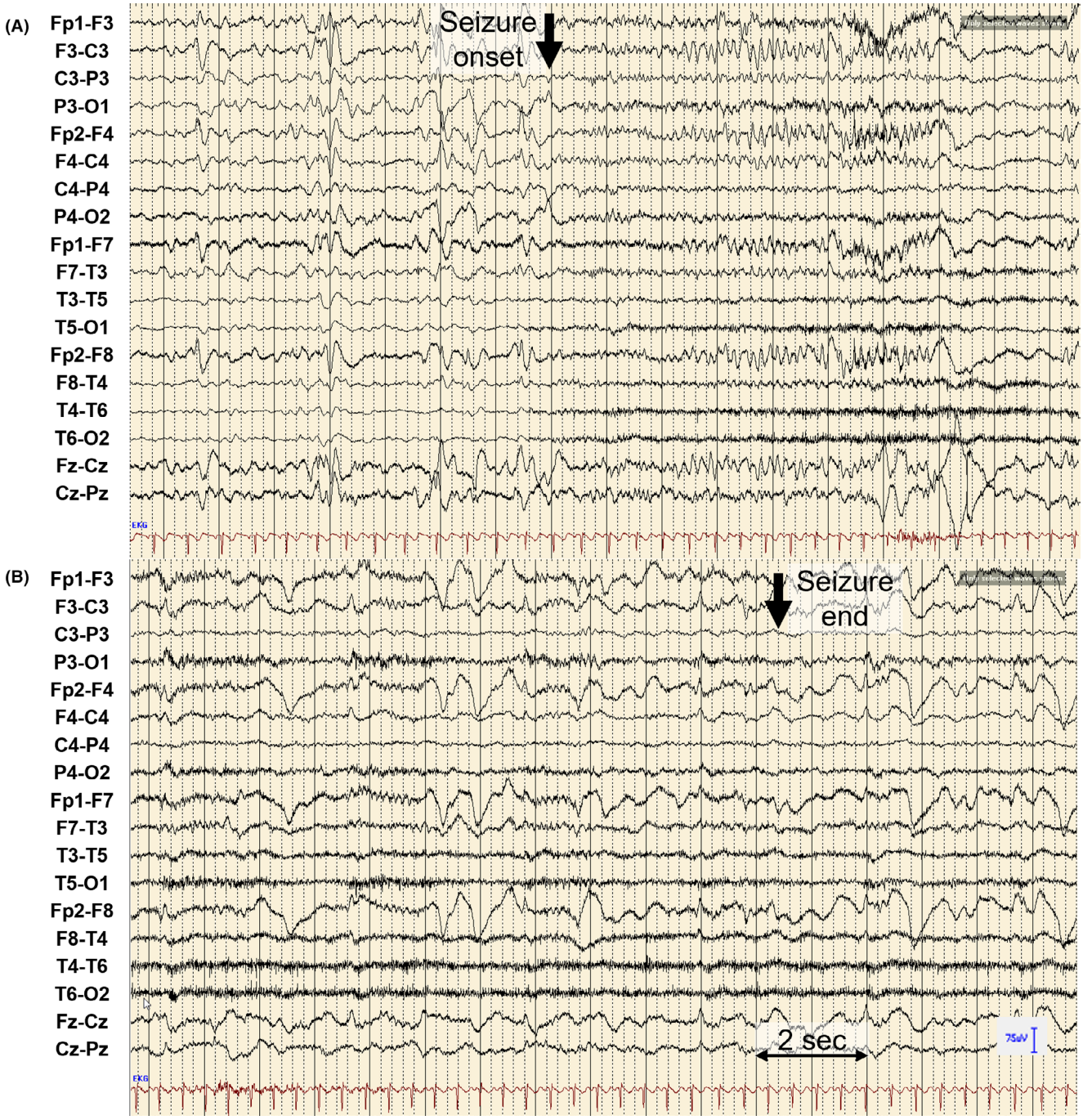

FIGURE 1 Ictal EEG: The seizure onset is shown in (A). Prior to electrographic onset (arrow), abundant interictal focal spikes and sharp waves are seen over the frontal regions. At seizure onset, there is diffuse attenuation, and diffuse low amplitude beta activity develops, with the ictal rhythm evolving to become maximal over the bilateral frontal regions. A marked increase in heart rate is seen. In (B), the seizure continues, but the ictal rhythm has a stuttering course, being briefly interrupted for 1–2 s at a time. After seizure conclusion, post-ictal delta slowing is observed over the frontal regions.

Head CT and MRI were both normal. Lumbar puncture at initial presentation showed normal cell count, glucose, and protein; viral and bacterial testing, as well as an encephalitis antibody panel, were all negative. An epilepsy gene panel including more than 2300 genes (GeneDx EpiXpanded panel) was performed on a peripheral blood sample, and identified a de novo mosaic novel *CLTC* in-frame deletion (c. 4744_4746del, p.(Val1582del) (NM_004859.3)), present in 23% of 53 sequencing reads. The variant is absent in control databases and classified as pathogenic per American College of Medical Genetics and Genomics criteria (PS2, PM1, PM2, and PM4).[8] The patient's family provided written consent for this publication.

This patient's presentation expands the phenotypic spectrum for *CLTC* pathogenic variants, as she is the first individual to be reported with normal intelligence. All 31 previously reported individuals with pathogenic *CLTC* variants had intellectual disability, ranging from mild to severe.[5–7]

The milder developmental phenotype presumably occurred because she has a mosaic pathogenic variant, and not all cells have CLTC dysfunction. However, the impact of the patient's specific variant may be relevant as well. Among the patients reported with CLTC-related disorder, variant types have included frameshift, in-frame, missense, nonsense, and splice site.[5–7] Epilepsy was more commonly reported in patients with missense variants or in-frame deletions, as was the case in the patient we report here; however, the degree of developmental impairment tended to be more severe in those patients as well, and structural brain abnormalities were more frequently observed.[6]

Our patient's seizures were focal aware with fear and tachycardia, with hyperkinetic movements sometimes seen as well. These features suggested a possible ictal focus in the insular-opercular or mesial temporal regions.[9] The pattern on scalp EEG showed interictal and ictal findings suggestive of an anterior focus, with seizures following an unusual stuttering pattern.

In conclusion, this study expands the phenotypic spectrum associated with *CLTC* pathogenic variants and demonstrates that this gene should be considered as a cause in patients with epilepsy, even in the absence of intellectual disability.

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CONFLICT OF INTEREST STATEMENT

M.A. Sveistrup reports no disclosures relevant to the manuscript. K.A. Myers is a site principal investigator for studies sponsored by Ultragenyx and LivaNova, and is on an advisory committee for Jazz Pharmaceuticals.

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REFERENCES

1. Dodge GR, Kovalszky I, McBride OW, Yi HF, Chu ML, Saitta B, et al. Human clathrin heavy chain (CLTC): partial molecular cloning, expression, and mapping of the gene to human chromosome 17q11-qter. Genomics. 1991;11:174–8.
2. Kaksonen M, Roux A. Mechanisms of clathrin-mediated endocytosis. Nat Rev Mol Cell Biol. 2018;19:313–26.
3. Royle SJ, Bright NA, Lagnado L. Clathrin is required for the function of the mitotic spindle. Nature. 2005;434:1152–7.
4. DeMari J, Mroske C, Tang S, Nimeh J, Miller R, Lebel RR. CLTC as a clinically novel gene associated with multiple malformations and developmental delay. Am J Med Genet A. 2016;170A:958–66.
5. Hamdan FF, Myers CT, Cossette P, Lemay P, Spiegelman D, Laporte AD, et al. High rate of recurrent De novo mutations in developmental and epileptic encephalopathies. Am J Hum Genet. 2017;101:664–85.
6. Nabais Sá MJ, Venselaar H, Wiel L, Trimouille A, Lasseaux E, Naudion S, et al. De novo CLTC variants are associated with a variable phenotype from mild to severe intellectual disability, microcephaly, hypoplasia of the corpus callosum, and epilepsy. Genet Med. 2020;22:797–802.
7. Itai T, Miyatake S, Tsuchida N, Saida K, Narahara S, Tsuyusaki Y, et al. Novel CLTC variants cause new brain and kidney phenotypes. J Hum Genet. 2022;67:1–7.
8. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405–24.
9. Martinez-Lizana E, Brandt A, Foit NA, Urbach H, Schulze-Bonhage A. Ictal semiology of epileptic seizures with insulo-opercular genesis. J Neurol. 2022;269:3119–28.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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Test yourself

1. The *CLTC* gene encodes what protein?
   A. Cell-lining transport channel
   B. Clathrin heavy chain 1
   C. C-related ladder transport channel
   D. Clathrin light chain 1
   E. Calcium light transfer channel
2. What percentage of patients reported with CLTC-related disorders have seizures?
   A. 100%
   B. 90%
   C. 65%
   D. 38%
   E. 12%
3. Which of the following is true regarding genotype-phenotype correlation in CLTC-related disorders?
   A. Seizures are more commonly reported in patients with missense variants or in-frame deletions
   B. Developmental impairment is milder in patients with missense variants or in-frame deletions
   C. Seizures are more commonly reported in patients with nonsense variants
   D. Structural brain abnormalities are more commonly reported in patients with nonsense variants

Answers may be found in the supporting information.