Epilepsy & Behavior Reports 13 (2020) 100355

Contents lists available at ScienceDirect

Epilepsy & Behavior Reports

journal homepage: www.elsevier.com/locate/ebcr

Case Report

Juvenile myoclonic epilepsy mimic associated with CHD2 gene mutation

Neeraj Singh [a], Anthony Ritaccio [b,*]

[a] Epilepsy Division, Department of Neurology, Albany Medical Center, United States of America
[b] Department of Neurology, Mayo Clinic Florida, United States of America

ARTICLE INFO

Article history:
Received 18 September 2018
Received in revised form 17 December 2019
Accepted 27 December 2019
Available online 07 January 2020

Keywords:
CHD2
Juvenile myoclonic epilepsy
JME
Autism spectrum disorder

ABSTRACT

This paper reports the electroclinical manifestations of an epilepsy syndrome associated with a chromodomain helicase DNA-binding protein 2 (CHD2) gene mutation with clinical semiology and electroencephalographic (EEG) features consistent with juvenile myoclonic epilepsy (JME). Myoclonic and myoclonic-tonic–clonic seizures, as well as generalized 4- to 5-Hz high-amplitude spike–wave and polyspike–wave discharges, were well characterized in an adolescent. However, the atypical age of onset, developmental disability, and apparent drug resistance led to suspicion of an alternative etiology for epilepsy, subsequently verified as a CHD2 gene mutation. When atypical features are present, a JME mimic should be suspected in the differential diagnosis of the more established syndrome of JME.

1. Introduction

Juvenile myoclonic epilepsy (JME) is one of the most common generalized epilepsy syndromes affecting youth, representing 10% of all epilepsy cases, and 25–30% of genetic generalized epilepsies [1]. Its mean age of onset is 15 years, with most individuals diagnosed between ages 12 and 18, although onset has been reported between ages 5 and 24 [2].

Typically, JME commonly presents with a triad of absence seizures, generalized tonic–clonic seizures, and myoclonic jerks, often with sleep deprivation or upon awakening. Given the different initial JME presentations, it may be confused with absence epilepsy or other forms of genetic generalized epilepsy [1,3]. Additionally, myoclonic jerks can be mistaken for presentations of other types of myoclonic epilepsy, many of which are progressive and not as easily controlled with anti-seizure medications [1,3]. To help distinguish JME from other types of epilepsy, it is important to consider the different seizure manifestations, age of onset, and comorbidities. For instance, even when the typical triad is seen, an age of onset younger than 12 and a history of developmental delay are less likely to be consistent with JME [3].

2. Case report

A 9-year-old boy with a known diagnosis of autism spectrum disorder since age 3 was brought by his father to the Emergency Department (ED) after being found on the floor, unresponsive in a pool of saliva with jaw clenched and eyes rolled back for approximately 20 min. Routine scalp EEG was normal. He was presumed to have had a generalized seizure and was initiated on levetiracetam with a total daily dose of 12 mg/kg per day (200 mg twice daily) and was reported seizure-free for over three years on that dose. At age 12, his mother brought him back to the ED after a clearly observed convulsion. Repeat EEG revealed generalized 4-Hz high-amplitude spike–wave and polyspike–wave discharges. A 3-tesla MRI of the brain was normal. Subsequently, the patient was switched to lamotrigine and titrated to a total daily dose of 5 mg/kg per day (150 mg twice daily). Although he had mild irritability on lamotrigine, he remained seizure-free for another three years. After a third seizure at age 16, he was brought back to the ED, and a subsequent routine EEG was normal.

The patient then underwent continuous video-EEG recordings at Albany Medical Center in Albany, NY, for a total EEG recording time of 51 h, without changes to lamotrigine dosage. This study revealed intermittent 5-Hz high-amplitude generalized spike–wave and polyspike–wave discharges (Fig. 1), similar to what was seen on his second routine EEG at age 12. Two electroclinical seizures were also captured. The first seizure involved unilateral upper extremity myoclonus for 1–2 s, time-locked with 5-Hz generalized polyspike–wave discharges. The second seizure, occurring within 2 min of the first one, involved bilateral upper extremity myoclonus followed by right head version, bilateral arm tonic extension, ictal cry, and then clonic movements. This was associated with generalized rhythmic delta slowing that evolved into a

Abbreviations: CHD2, chromodomain helicase DNA-binding protein 2; CLCN2, chloride channel protein 2; ED, emergency department; EEG, electroencephalogram; EFHC1, EF-hand domain containing protein 1; GABRA1, gamma-aminobutyric acid type A receptor alpha 1 subunit; JME, juvenile myoclonic epilepsy; TIGER, the Investigation of Genetic Exome Research; WES, whole exome sequencing.

* Corresponding author at: Mayo Clinic Neurology, 4500 San Pablo Rd S, Jacksonville, FL 32224, United States of America.
E-mail address: ritaccio.anthony@mayo.edu (A. Ritaccio).

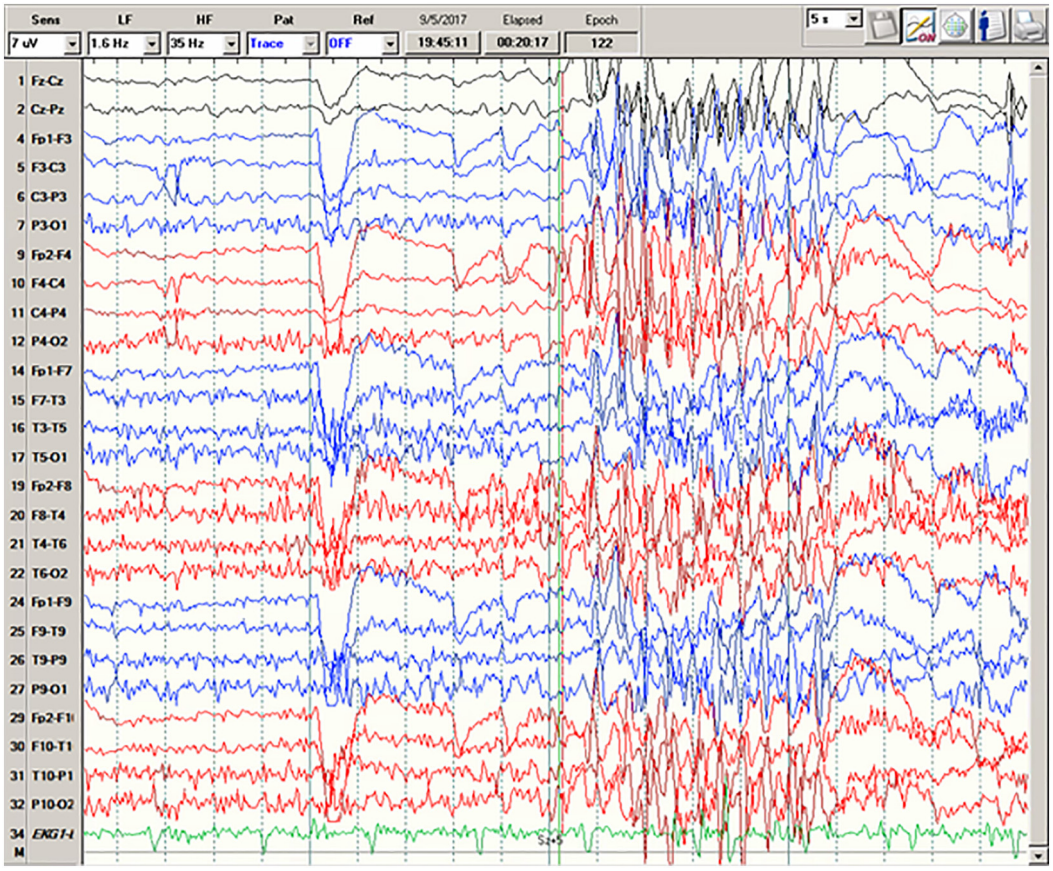

Fig. 1. Interictal 5-Hz generalized polyspike-wave discharges seen during this patient's continuous video EEG recording.

train of 5-Hz generalized spike-wave activity as part of typical EEG features during tonic-clonic activity.

Based on the continuous video-EEG results, 500-mg extended-release valproate was added to his anti-seizure medication regimen. The extended-release lamotrigine dosage was decreased to 200 mg once daily given its increased bioavailability when co-administered with valproate. One year after these medication changes were made, the patient remained seizure-free.

Given the history of autism spectrum disorder with epilepsy, whole exome sequencing (WES) was performed through the Investigation of Genetic Exome Research (TIGER) study at the University of Washington. This revealed a substitution of thymine for cytosine in the long arm of chromosome 15. This resulted in a nonsense mutation that led to early termination of CHD2 protein translocation. Comparison with his parents' WES results revealed that this was a de novo mutation. This mutation was suspected to be associated with the patient's seizures because other mutations typically seen with JME were not detected with WES.

3. Discussion

The patient's epilepsy initially appeared to meet criteria for juvenile myoclonic epilepsy (JME), given the predominance of myoclonic jerks, high-frequency generalized spike-wave and polyspike-wave activity on EEG, and a recorded myoclonic–tonic–clonic seizure during long-term video-EEG monitoring. However, additional atypical findings called this diagnosis into question. First, the patient presented with his first seizure at age 9, and had previously experienced brief episodes of unresponsiveness that may have been undiagnosed absence seizures as early as age 6. Although JME cases have been reported at this young age, they are uncommon [2,3]. Additionally, JME has not been shown to be associated with CHD2 mutations to our knowledge. Instead, JME is mostly associated in mutations in genes for the gamma-aminobutyric acid type A receptor alpha 1 subunit (GABRA1) on chromosome 5, which can affect the $GABA_A$ receptor structure; the EF-hand domain containing protein 1 (EFHC1/ Myoclonin1) on chromosome 6, which can impair calcium movement across cell membranes; and the chloride channel protein 2 (CLCN2) on chromosome 3, which can interfere with formation of chloride channels [4]. New mutation associations with JME continue to be discovered, most recently involving bromodomain-containing protein 2 (BRD2) on chromosome 6, which affect nuclear protein transcription, and connexin-36 (Cx-36) on chromosome 15, which affect formation of interneuronal channels [4]. The CHD2 mutations, on the other hand, have established associations with Lennox–Gastaut, Dravet, and Jeavons syndromes, although this patient's electrographic findings did not meet criteria for these [5,6].

4. Conclusion

This JME mimic represents a unique genetic epilepsy that may share a common clinical and electrical phenotype with JME. However, the early age of seizure onset and the existing diagnosis of autism spectrum disorder made the diagnosis of JME questionable. The novel genetic basis for this child's epilepsy may have been the determinant for his resistance to medications that are commonly effective in treating JME as monotherapy. While JME is a fairly well-established syndrome to neurologists and epileptologists, its electroclinical features are not exclusive and alternative diagnoses must be considered, especially when atypical historical features are present, to ensure appropriate therapy and prognosis is provided to the patient.

References

[1] Hauser WA. The prevalence and incidence of convulsive disorders in children. Epilepsia 1994;35(Suppl 2:S1).
[2] Jayalakshmi SS, Srinivasa Rao B, Sailaja S. Focal clinical and electroencephalographic features in patients with juvenile myoclonic epilepsy. Acta Neurol Scand 2010 Aug; 122:115–23.
[3] Canevini MP, Mai R, Di Marco C, Bertin C, Minotti L, Pontrelli V, et al. Juvenile myoclonic epilepsy of Janz: clinical observations in 60 patients. Seizure 1992;1:291.
[4] Delgado-Escueta AV. Advances in genetics of juvenile myoclonic epilepsies. Epilepsy Curr 2007;7(3):61.
[5] Lund C, Brodtkorb E, Øye AM, Røsby O, Selmer KK. CHD2 mutations in Lennox-Gastaut syndrome. Epilepsy Behav Apr 2014;33:18–21.
[6] Suls A, Jaehn JA, Kecskés A, Weber Y, Weckhuysen S, Craiu DC, et al. De novo loss-of-function mutations in CHD2 cause a fever-sensitive myoclonic epileptic encephalopathy sharing features with Dravet syndrome. Am J Hum Gen Nov 2013;93:967–75.