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A Case of a Seven-Year-old boy with Epilepsy with Myoclonic Absence: Importance of Seizure Semiology, Genetic Etiology, and Electroencephalogram Correlation for Timely Intervention

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Abstract

Epilepsy with myoclonic absence (EMA) is a rare disorder with a mean age of onset of 7 years. It is characterized clinically by rhythmic, myoclonic jerking of the head, extremities or both, with impairment of consciousness and an ictal electroencephalogram (EEG) pattern of 3 Hz bilateral, synchronous and symmetrical spike and wave discharges. Prognosis is guarded and most patients are pharmaco-resistant. We present a case of EMA, found to have a FOXP1 gene pathogenic variation and a variance of unknown significance in the MBD5 gene, who was admitted to the intensive care unit in super-refractory status epilepticus. Given the overlap in symptoms of syndromes including myoclonic-astatic epilepsy, childhood absence epilepsy and juvenile myoclonic epilepsy, a detailed seizure semiology with EEG correlation, cannot be over emphasized. In this case, the genetic etiology may lend an interesting insight to the severity and prognosis.

Keywords

antiseizure drugs, children, electroencephalography, genetics, refractory, status epilepticus

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Introduction

Epilepsy with myoclonic absence (EMA), also known as Tassinari syndrome, was first described by Tassinari, et al in 1969. It was accepted as an individualized syndrome by the Commission on Classification and Terminology of the International League Against Epilepsy on 1989.[1] It is classified as a cryptogenic or symptomatic epilepsy syndrome, with an estimated incidence of 0.5–1% of patients referred to a specialized epilepsy center.[2] EMA is a specific seizure type involving involuntary muscle contraction of the head, extremities or both, associated with impairment of consciousness of variable intensity. The EEG consists of 3-Hz generalized spike and wake discharges.[3,4] The duration of the seizure ranges from approximately 10 to 60 s with a frequency of several times per day. The etiology is unclear; however, it has been linked to trisomy 12p, inv dup (15), Angelman syndrome and potassium channelopathies. Episodes of EMA status epilepticus have rarely been reported.[3]

Features that differentiate childhood absence epilepsy (CAE) from EMA, are that typical absence seizures occur in neurotypical school-age children, presenting with sudden loss of consciousness without loss of tone. Seizure semiology is subtle with staring, motor automatisms, and eyelid movements and the duration of seizures is shorter, but more frequent, occurring tens of times per day.[1] Extremity myoclonias in a

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child with neurodevelopmental delay, should raise concerns for other types of seizures rather than CAE.

Case

We report a seven-year-old male, with history of mild developmental delays, attention-deficit/hyperactivity disorder (ADHD) and well-controlled absence seizures with valproic acid. He presented with 3 Hz generalized spike and wave status epilepticus (Figure 1) with change in usual seizure semiology to prolonged episodes of staring spells associated with eyelid, lip and proximal upper extremity myoclonia. At the time of presentation, the patient was witnessed having 20 cluster of seizures per day, with each cluster lasting 6 to 20 min. The status epilepticus was refractory to lorazepam, valproic acid (VPA), levetiracetam, ethosuximide (ESM), topiramate, clobazam, and pyridoxine. He continued to have subclinical super-refractory status epilepticus while on midazolam and propofol drips. Burst-suppression was achieved by pentobarbital infusion, but status epilepticus recurred in weaning attempts. Neuroimaging did not reveal cortical dysplasia, acute insults or structural abnormalities. Epilepsy gene panel showed a variant of unknown significance in the MBD5 gene, variant c.2903C > T(p.Ser968Leu), and the chromosome microarray detected a copy number loss within chromosome band 3p13 spanning approximately 0.056 Mb in size involving exon 5 of the FOXP1 gene. The patient was transferred to an outside hospital on pentobarbital infusion for further care. He required pentobarbital infusion for a total of 12 days, while on therapeutic hypothermia. He suffered moderate deficits in neurocognition and motor skills after resolution of status epilepticus and was discharged home on clobazam, ESM, lacosamide, and VPA. He required a gastrostomy tube and is non-ambulatory.

His epilepsy has remained refractory and his anti-seizure medications as an outpatient have expanded to include cannabidiol and rufinamide. He is being evaluated to start a ketogenic diet and due to worsening abnormal behaviors including self-aggression, hyperactivity, sleep disturbance and oppositional-defiant behavior, patient is being trialed on combination of amphetamine/dextroamphetamine, olanzapine and lithium.

Discussion/Conclusion

This case of EMA with pathogenic FOXP1 gene mutation and variance of unknown significance found on the MBD5 gene, adds to the literature with its unique presentation of super-refractory status epilepticus in a child with mild intellectual disability, ADHD and previously well controlled epilepsy. It underscores the importance of a careful description of seizure semiology with electroclinical correlation and genetic testing. Literature review showed a proposed association between MBD5 gene mutation, FOXP1 gene mutation and neurodevelopmental disorder, as well as MBD5 gene mutation and non-convulsive status epilepticus. Thus our case report adds to the body of evidence that the above-mentioned genes may play a more critical role in the etiology and prognosis of EMA with intellectual disability and status epilepticus. Routine genetic testing in refractory epilepsy may further our understanding of these enigmatic genes.

In two-third of cases, EMA have been preceded by other seizure types and/or have been found in association with other seizure types, such as simple absences and generalized tonic-clonic seizures.[3] One of the largest series of patients with EMA found a male preponderance of 60–70% of the 51 patients studied,[2] contrary to the usual female prevalence found in CAE. Patients with EMA, usually present with intellectual disability or learning difficulties

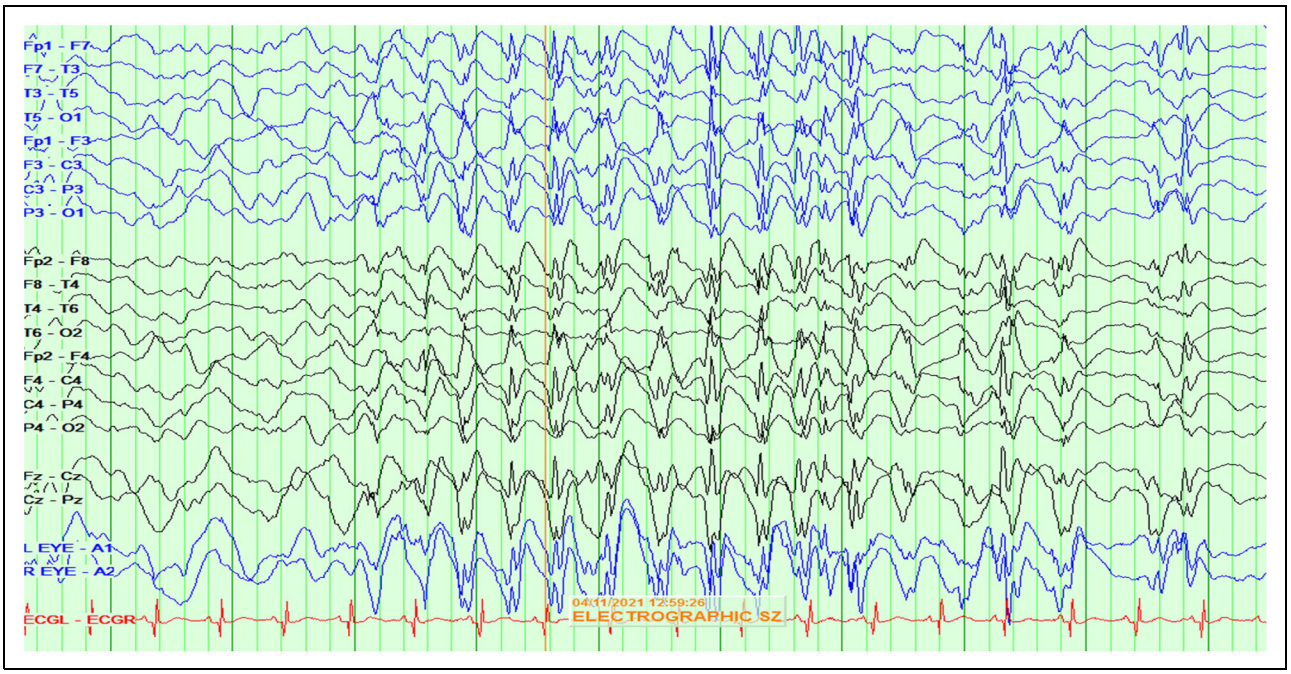

Figure 1. EEG on admission.

Table 1. Description of Epileptic Syndromes that Overlap with Epilepsy with Myoclonic Absences. SZ: Seizure.

	Epilepsy with myoclonic absences (EMA)	Childhood absence epilepsy (CAE)	Myoclonic-astatic epilepsy	Juvenile myoclonic epilepsy (JME)
Definition	-Absence seizures accompanied by rhythmic myoclonias of face and upper extremities -Complete or partial loss of consciousness -Duration 10 – 60 s	Absences, with loss of awareness	Myoclonic-atonic seizures	-Bilateral, single or repetitive, arrhythmic, irregular myoclonic jerks, predominantly in arms -Shortly after awakening
Ictal EEG	-Bilateral, synchronous and symmetrical spike and wave discharges repeated at 3 Hz -Myoclonias on EMG	Bilateral, synchronous and symmetrical spike and wave discharges repeated at 3 Hz	-Often normal EEG. -EEG with slowing of the background, 4 – 7 Hz rhythms, irregular fast spike-wave or polyspike wave	>3-Hz spike or polyspike waves with frontocentral predominance
Additional features	-Male preponderance -Intellectual disability -Associated sz: simple absences, clonic seizures, drop attacks and GTCS	-Female preponderance -Normal intellect -No other sz types associated	-Normal development or delay in only one domain before epilepsy onset -Poor cognitive outcomes	-Normal development -Associated seizures: GTC or absences -GTCs occur in nearly all people with JME
Treatment	-Valproate and ethosuximide -Can develop refractory epilepsy	-Ethosuximide -Good response to monotherapy	-Valproic acid -Ketogenic diet -Can develop refractory epilepsy	Valproate

before the onset of symptoms.[5] In CAE, children have a normal intellect, respond well to monotherapy, and have a favorable long-term prognosis (see Table 1). CAE with myoclonias is also a well-recognized variant, but myoclonias in CAE are typically restricted to facial areas such as eyebrows, eyelids, perioral regions and chin, while EMA has a constant and prominent involvement of proximal upper extremities.[3]

While the treatment of EMA is not well established, a combination of VPA and ESM, have been found to be effective for myoclonic absences without any other associated seizures, especially generalized tonic clonic seizures (GTCS).[3] Manonmani and Wallace showed that the combination of VPA or ESM with lamotrigine had synergistic effect on children resistant to the classical treatment of VPA and ESM. Verotti, et al, studied 6 patients with early onset EMA. Three of their patients required polytherapy for seizure control with combination of ESM and clonazepam; ESM and VPA; clonazepam, phenobarbital and VPA, while the rest achieved complete seizure control with VPA monotherapy.[6] Topiramate and zonisamide may hold promise in EMA as adjunct therapy.[7]

Approximately 20% of patients with EMA have an associated pathogenic variant and 12% have a family history of epilepsy.[8] Elia, et al linked EMA to chromosome abnormality syndromes, such as inv dup (15) presenting with a Prader Willi Syndrome phenotype, trisomy 12p and Angelman Syndrome. On review of the literature, a copy number loss within chromosome 3p13, involving the FOXP1 gene has not been connected with EMA yet. A heterozygous mutation in the FOXP1 gene has been associated with intellectual disability with language impairment,[9] as found in our patient. Moreover, Myers, et al found a diverse spectrum of seizure phenotypes, including myoclonic, atonic, absence, tonic-clonic seizures linked to MBD5 gene mutation in studied subjects. This genetic variant was recognized often to be associated with severe early childhood-onset developmental and epileptic encephalopathy. Neuropsychiatric and developmental features were prominent including moderate to severe developmental delay, language deficits, sleep disturbance, hyperactivity and aggression, as also found in our patient.[10,11]

The anamnestic description of EMA may be difficult: the rhythmic myoclonic movements can be overlooked, especially if there is a tonic component associated with them.[3] Supplementary studies with electromyographic and electroencephalographic recordings, to aid in the quantification and location of motor activity may be warranted. The long-term prognosis of EMA is not clearly defined. The continuation of seizures, mild to moderate learning difficulties, and, for most of patients, restless and problematic behavior has made appropriate social integration challenging.[5]

We emphasize the importance of genetic testing for early onset and intractable epileptic encephalopathies. Testing can aid in the early identification of the epilepsy syndrome, which can provide valuable information on prognosis and management.[12] Given the unclear trajectory of these patients, consider early involvement of a multidisciplinary team including neurology, genetics, and neurodevelopmental pediatrics for screening and appropriate follow up of children with EMA. Further study of this fascinating syndrome is needed to better understand optimal management and improve outcomes.

Author Contributions

IF and SFA conceived of the presented idea. IF devised the project,the main conceptual ideas and proof outline as well as wrote the manuscript with support from SA and SFA. SFA supervised the project.

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Trial Registration

This manuscript does not involve a clinical trial.

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