Seizure: European Journal of Epilepsy 71 (2019) 158–160

Contents lists available at ScienceDirect

Seizure: European Journal of Epilepsy

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

Clinical letter

Jeavons syndrome in a family with GLUT1-deficiency syndrome

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ARTICLE INFO

Keywords:
Jeavons syndrome
Eyelid myoclonia
Hypoglycorrhachia
Ketogenic diet
SLC2A1

1. Introduction

Glucose transporter-1 (GLUT1)/SLC2A1 is expressed at the highest levels in brain capillaries, astroglia, and erythrocytes. GLUT1-deficiency syndrome is a neurological disorder resulting primarily from aberrant glucose transport into the brain. Clinically, it is classified as GLUT1-deficiency syndrome with epilepsy and without epilepsy. The phenotypic spectrum of GLUT1- deficiency syndrome expanded over last two decades, encompassing a varying combination of epilepsies (absence, atypical absence, myoclonic, myoclonic-astatic, refractory generalized epilepsy, intractable infantile epilepsy etc.), movement disorders (paroxysmal exercise-induced dyskinesia, ataxia, etc.), and developmental delay.

Pointers to diagnosis include a classical phenotype: early-onset absences, fasting-induced paroxysms (clinical and electroencephalographic), low cerebrospinal fluid (CSF) glucose (< 50 mg/dl; CSF to blood glucose ratio < 0.6) and lactate (< 1.4 mmol/L), and a remarkable response to ketogenic diet (KD) [1]. Early diagnosis and treatment are rewarding. This report adds a novel presentation to the evolving phenotype of GLUT1-deficiency syndrome.

2. Case report

A 9-year-old boy presented with delayed attainment of developmental milestones and intractable seizures (since the age of 4 months). The perinatal period was uneventful. He was born of a non-consanguineous marriage. Father had concomitant squint, subnormal intelligence, and a history of infantile-onset generalized epilepsy. He had generalized tonic-clonic seizures twice a month, which subsided by adolescence (details of antiepileptic drug (AED) therapy were not available). Paternal uncle also had childhood-onset epilepsy, however further details could not be obtained (pedigree as supplementary Fig. 1). During infancy, the child used to have infrequent multifocal seizures and paroxysms of intermittent involuntary gaze. By 3 years of age, he started having frequent absences with eyelid myoclonia, which were refractory to multiple AEDs- valproate, phenobarbital, benzodiazepines, phenytoin and topiramate. He also had mild intellectual disability (IQ-62), gait ataxia, and scanning speech. Head circumference was 49 cm (-1 to -2 SD). Sleep electroencephalography (EEG) done at outside facility showed multifocal interictal discharges.

Metabolic profile (blood ammonia, acyl carnitine, arterial lactate, urine organic acids) and brain MRI was normal. EEG revealed a normal background, eye-closure sensitivity (eye-closure triggered eyelid-myoclonia with absences) (Fig. 1), and photosensitivity (Fig. 2) suggestive of Epilepsy with eyelid myoclonia and absences (EMA; Jeavons Syndrome). CSF analysis revealed hypoglycorrhachia (CSF: blood glucose = 0.32) with a subnormal CSF lactate (1 mmol/l; normal: 1.2–2.1 mmol/l). Targeted gene sequencing revealed a heterozygous missense pathogenic variation in exon 4 of *SLC2A1* gene (chr1:43396437; G > G/A) resulting in the substitution of cysteine for arginine at codon126 (*p.Arg126Cys*) in both child and his father. *R126* is a known mutational hotspot in *SLC2A1* gene and the observed variation (*R126C*) has been reported previously [2,3]. The child had a dramatic response to KD with complete seizure remission within 4 weeks of its initiation. His motor coordination and gait improved alongwith a 10point improvement in IQ over a year.

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https://doi.org/10.1016/j.seizure.2019.07.011
Received 19 April 2019; Received in revised form 12 June 2019; Accepted 11 July 2019

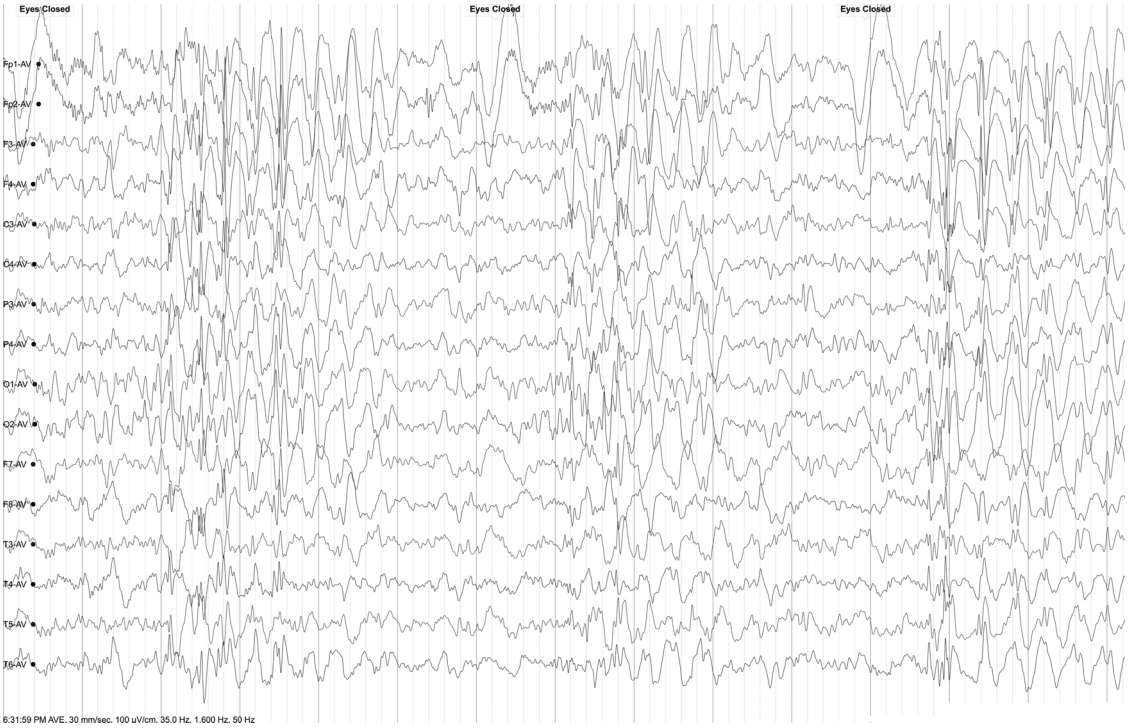

Fig. 1. EEG of the index patient.
Legend: 10 s EEG epochs (referential montage; sensitivity: 100uV; sweep speed:30 mm/s) showing 2–3 Hz spike–slow waves(generalized) with leading occipital spikes following voluntary eye-closure.

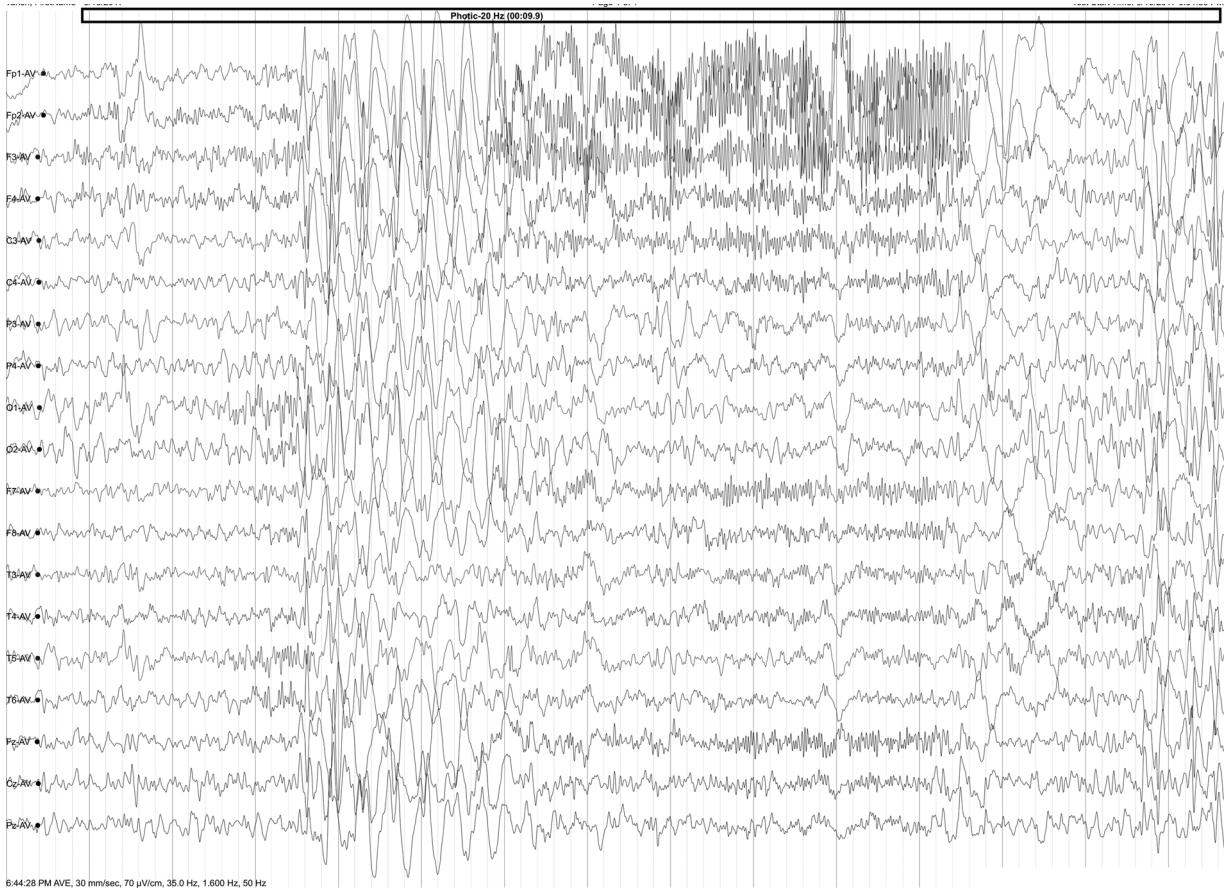

Fig. 2. EEG of the index patient with intermittent photic stimulation.
Legend: 10 s EEG epoch (referential montage; sensitivity: 70uV; sweep speed: 30 mm/s) shows a photoparoxysmal response (PPR) and photomyogenic response at 20 Hz intermittent photic stimulation.

3. Discussion

The clinical phenotype of an uncommon, difficult-to-diagnose, drug-refractory epilepsy syndrome (EMA) with an underlying rare but potentially treatable genometabolic condition (GLUT1-deficiency syndrome) makes this case report interesting.

EMA is a rare life-long epilepsy syndrome without any identified underlying genes. Primarily an electroclinical diagnosis, it is a triad of eyelid myoclonia with or without absences, photosensitivity, and eye-closure sensitivity. The absence of evident convulsive seizures makes its recognition difficult. The lead time to diagnosis is often prolonged and response to AED is usually unsatisfactory [4]. To the best of our knowledge, none of the reported cases of EMA had GLUT1-deficiency syndrome. Autosomal dominant inheritance, early-onset absences, cognitive delay, and ataxia prompted an evaluation for GLUT1-deficiency syndrome in the index patient.

GLUT1-deficiency syndrome is a recently established, potentially treatable disorder with varied presentation ranging from epilepsy to movement disorder. Misdiagnosis is common but detrimental. Therefore, clinicians should be aware of each manifestation of this rare disorder. Similar to the previously reported patients with *R126C* variant, the index family had an epilepsy-dominant phenotype with subnormal intelligence and cerebellar signs [1]. *R126C* variant has been associated with typical absences, myoclonic absences and myoclonic seizures [1]. The eye-closure and photosensitivity in the index case were novel. Future research regarding the susceptibility of different networks in different patients might add to pathogenetic mechanisms underlying GLUT1-deficiency syndrome.

The index case exemplifies the ever-expanding spectrum of GLUT1-deficiency syndrome.

4. Conclusion

Unearthing the underlying genetic-metabolic etiology is as important and rewarding as identifying the correct epilepsy syndrome. A high index of suspicion, appropriate utilization of molecular genetics and precision medicine are prerequisites for a successful outcome in treatable metabolic disorders such as GLUT1-deficiency syndrome presenting as rare epilepsy syndromes.

Financial disclosures

None.

Statistical analysis

Not applicable.

Consent

Written informed consent obtained from parents of the patient.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Authors' contribution

PM: Patient management, literature review, and initial draft manuscript preparation; PJ: Patient management, concept and design of the study, critical review of manuscript, and final approval of the version to be published; BC & SG: Critical review of manuscript for important intellectual content and final approval of the version to be published

Declaration of Competing Interest

None.

Acknowledgements

Authors thank the parents of the patient for agreeing to add to the scientific literature

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2019.07.011.

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