CASE REPORT

Hemimegalencephaly and Epileptic Encephalopathy Associated with a Variant of Uncertain Significance of the TRIO Gene

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Abstract

Objectives: Electrical status epilepticus during sleep (ESES) is a type of EEG pattern seen in children with childhood-onset epileptic seizures and cognitive, language and motor regression. ESES has been associated with different etiologies, with or without structural abnormalities of the brain. To replace the term "ESES", the recent Position Paper of the ILAE Taskforce on Nosology and Definitions introduced the term Epileptic Encephalopathy with Spike-Wave Activity during Sleep (EE-SWAS), which represents an activation of epileptiform activity, typically 1.5-2.5 Hz during NREM sleep, in a previously normal child and leads to cognitive and motor regression. Pathogenic variants in the TRIO gene are associated with autosomal dominant mental retardation type 44 (MRD44), which is characterized by mildly delayed global development resulting in variable intellectual deficits, learning difficulties, and variable dysmorphic features mostly represented by facial asymmetry, microcephaly, abnormalities of the fingers, and dental anomalies. **Materials and methods:** We present the case of a 13-year-old girl with onset of atonic seizures at the age of 3 who had undergone different types of antiepileptic drug (AED) therapies and was seizure-free 4 years later. She had an acquired impaired cognitive status as well as hemimegalencephaly, multiple hypopigmented patches on her legs and a large patch of hypopigmentation on the left side of her face extending towards the scalp (Becker's nevus), dental anomalies (gingival hyperplasia, ogival palate), periventricular gliosis and electroencephalographic and (EEG) findings consistent with SWAS. **Outcomes:** Genetic testing confirmed a heterozygous variant of uncertain significance (VUS) of the TRIO gene, possibly associated with autosomal dominant MRD44. Although our patient presented with some phenotypic similarities to MRD44, her cognitive impairment improved with control of the SWAS pattern and AED adjustments. **Conclusion:** Association of structural anomalies of white matter, hemimegalencephaly, and encephalopathy with SWAS and a VUS mutation of the TRIO gene might suggest a different genetic neurocutaneous syndrome altogether.

Keywords: hemimegalencephaly, ESES, EE-SWAS, VUS, TRIO.

Rezumat

Obiective: Statusul epileptic electric de somn (ESES) reprezintă un tip particular de traseu electroencefalografic, evident în cazul copiilor cu crize epileptice şi regres în dezvoltarea motorie, cognitivă şi de limbaj. ESES a fost asociat cu etiologii multiple, cu sau fără anomalii structurale. Ca urmare a ultimei lucrări elaborate de către Comisia de Nosologie şi Definiții a Ligii Internaționale de Luptă Împotriva Epilepsiei (ILAE), s-a introdus termenul de encefalopatie epileptică cu complexe vârf-undă în timpul somnului (EE-SWAS) pentru a înlocui termenul ESES, reprezentând accentuarea activității epileptice de 1,5-2,5 Hz în timpul somnului, la un copil anterior normal, care poate duce la regres motor şi cognitiv. Variantele mutaționale patogene la nivelul genei TRIO sunt asociate cu retardul mental autozomal dominant tipul 44, caracterizat prin uşoară întârziere în dezvoltarea globală, cu afectare intelectuală în diferite grade, tulburări de învățare şi diverse elemente de dismorfism facial precum asimetrie facială, microcranie

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sau anomalii ale degetelor şi ale danturii. **Materiale şi metode:** Prezentăm cazul unei adolescente de 13 ani cu crize epileptice atone debutate la vârsta de 3 ani pentru care s-au încercat diverse scheme de medicație antiepileptică care au dus la remiterea crizelor 4 ani mai târziu. Pacienta prezenta deficit cognitiv dobândit, hemimegalencefalie, multiple pete acrome la nivelul membrelor inferioare şi la nivelul hemifeței stângi cu extindere spre scalp (nev Becker), anomalii dentare (hiperplazie gingivală, boltă ogivală), leziuni gliotice periventriculare şi modificări EEG sugestive pentru SWAS. **Rezultate:** Testarea genetică a relevat o variantă heterozigotă cu semnificație incertă la nivelul genei TRIO care poate fi asociată cu retardul mental autozomal dominant tipul 44 (MRD 44). Deşi pacienta prezenta câteva elemente fenotipice sugestive pentru MDR 44, statusul ei cognitiv s-a îmbunătățit odată cu ameliorarea traseului EEG şi dispariția SWAS, dar şi cu ajustarea schemei terapeutice. **Concluzii:** Ridicăm ipoteza că asocierea hemimegalencefaliei, a anomaliilor structurale de substanță albă şi encefalopatiei cu SWAS, cu o mutație la nivelul genei TRIO, poate sugera un nou sindrom neurocutanat.

Cuvinte-cheie: hemimegalencefalie, ESES, EE-SWAS, VUS, TRIO.

OBJECTIVES

Encephalopathy associated with electrical status epilepticus during sleep (ESES) is a childhood-onset epileptic syndrome characterized by seizures, cognitive regression, and marked activation of epileptiform activity during non-rapid eye movement (NREM) sleep which produces an electroencephalographic (EEG) pattern of near-continuous spike-wave discharges[1-5]. ESES has been associated with different etiologies, with or without structural abnormalities of the brain. Thalamic lesions in the early stages of neurodevelopment have been particularly correlated with ESES[6-7]. Other genetic etiologies that have been associated with ESES include monogenic mutations (SCN2A, SLC9A6, GRIN2A, etc.) or genetic mutations linked with possible disfunction of NMDA-receptor mediated signaling[8-9].

The recent 2022 Position Paper of the ILAE Taskforce on Nosology and Definitions introduced the term Epileptic Encephalopathy with Spike-Wave Activity during Sleep (EE-SWAS) to replace the term "ESES". The term EE-SWAS represents the activation of epileptiform activity, typically 1.5-2.5 Hz during NREM sleep, in a previously normal child, which leads to cognitive and motor regression[1].

The TRIO gene on chromosome 5 has recently been associated with neurodevelopmental delay. TRIO acts as a major regulator of neuronal development by controlling actin cytoskeleton remodeling and is highly expressed in the cerebellum, cortex, hippocampi and thalami[10]. Pathogenic variants in the TRIO gene are associated with autosomal dominant mental retardation type 44, which is characterized by mildly delayed global development that results in variable intellectual deficits, learning difficulties and highly variable dysmorphic features mostly represented by facial asymmetry, microcephaly, abnormalities of the fingers, and dental anomalies[11-15]. TRIO gene variants of uncertain significance (VUS) might bring about other additional features or express none whatsoever[16-17].

Our objective is to describe an uncharacteristic phenotype marked by epileptic encephalopathy with SWAS and atonic seizures, hemimegalencephaly, cognitive impairment and speech delay, abnormalities of skin pigmentation and structural anomalies of periventricular white matter associated with a heterozygous VUS of the TRIO gene.

MATERIALS AND METHODS

We present the case of a 13-year-old girl who was first admitted to our clinic in October 2018 at the age of 11 for a second opinion on her epileptic disorder. Her seizure onset occurred at the age of 3 years, when she had her first atonic seizure. Her brain MRI revealed a slight enlargement of the left ventricle, possibly due to a periventricular white matter lesion, suggestive of gliosis.

Subsequent cerebral MRIs showed a minimal progression of the left periventricular gliosis with the appearance of periventricular cysts.

Initial AED regimen consisted of valproic acid, levetiracetam and clobazam, but seizure frequency remained around 1–2 seizures/month of prolonged duration and associated severe apnea which, in one case, required cardio-pulmonary resuscitation.

By the time she reached the age of 6, topiramate had been added to the AED regimen with good response, and our patient managed to remain seizure-free for about 2 years, until an attempt was made to withdraw Clobazam and the patient had a GTC seizure. Cloba-

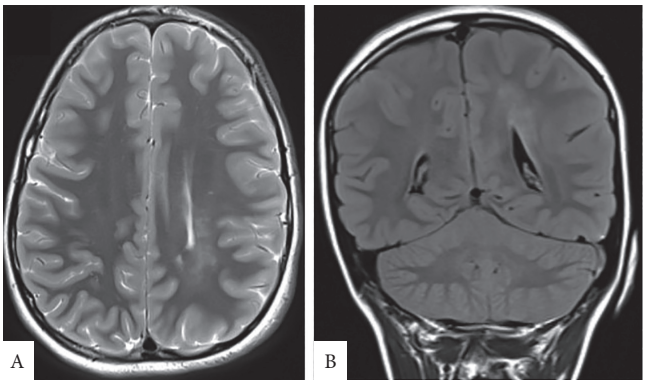

Figure 1. (A) Axial and (B) coronal view of left hemimegalencephaly with periventricular gliotic lesions - 3 T brain MRI

zam was reintroduced, and she has been seizure-free since then.

The family came to our clinic when the child had been seizure-free for 2 years. At the time, her mother described that there had been an onset of cognitive impairment in 2013, when the patient was 6 years old and already on AED treatment.

Clinical examination revealed multiple hypopigmented macules on her legs and a large patch of hypopigmentation on the left side of her face that extended to the scalp – a Becker's nevus. She also had gingival hyperplasia and an ogival palate but otherwise had a normal clinical examination. The neurological examination was normal.

The EEG at the time revealed SWAS, which regressed under corticotherapy. Otherwise, EEG abnormalities were consistent with focal, left, central discharges during sleep.

We performed a 3T MRI, which revealed cranial and cerebral asymmetry of the left hemisphere and ventricle consistent with hemimegalencephaly, gyral asymmetry and periventricular gliosis reaching the cor-

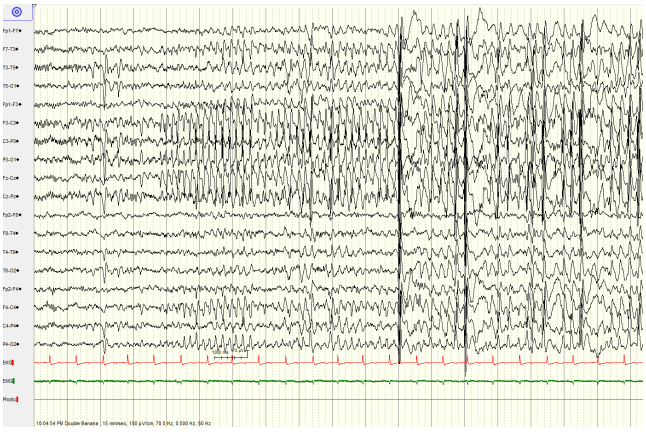

Figure 2. Initial EEG recording – wakefulness – marked asymmetry of epileptiform discharges, with focal SW over the left leads.

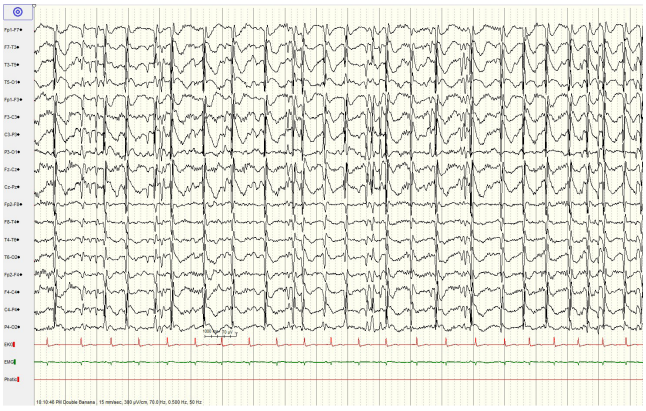

Figure 3. Initial EEG recording – sleep – SWAS.

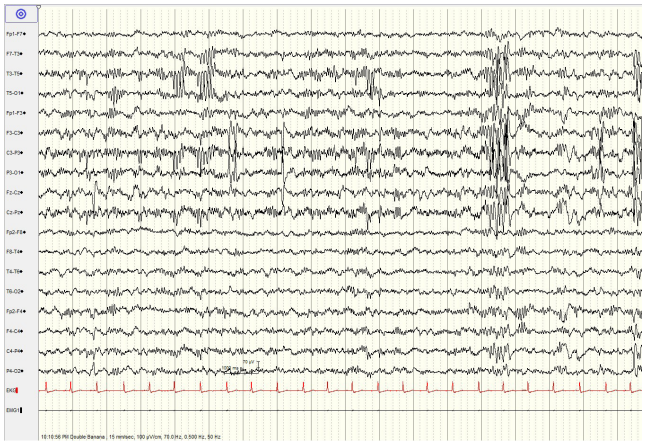

Figure 4. Follow-up EEG recording after treatment – wakefulness – reduction in SW frequency and interhemispheric asymmetry.

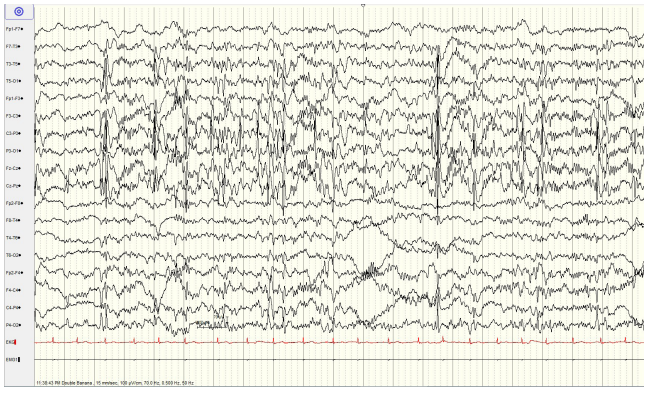

Figure 5. Follow- up sleep EEG recording after treatment – no SWAS, focal SW discharges over left leads, asymmetrical appearance

tex predominantly on the left hemisphere (Figure 1).

Genetic testing by array comparative genomic hybridization (CGH) was negative but whole-exome sequencing (WES) analysis revealed a heterozygous VUS (variant of uncertain significance) of the TRIO gene, situated on chromosome 5. The TRIO missense variant c.2335A>G p.(Lys779Glu), exon 13, is responsible for an amino acid change from Lys to Glu at position 779.

OUTCOMES

We suspected a possible genetic syndrome with a particular phenotype including structural cerebral, cranial, and facial abnormalities, focal epilepsy, and encephalopathy associated with a particular EEG trace: SWAS, a marked interhemispheric asymmetry and left focal epileptic discharges (Figure 2, Figure 3). The EEG anomalies, i.e. SWAS, were significantly reduced in subsequent EEG recordings (Figure 4, Figure 5). More importantly, the patient remained seizure-free and her cognitive status had drastically improved.

Initial treatment with valproic acid was not tolerated, yet she responded well to AED combination therapy with levetiracetam, benzodiazepine (clobazam), and topiramate. After she had been seizure-free for about 2 years, the decision was made to reduce the doses of benzodiazepines because her cognitive status had started to decline. The dosage reduction led to a tonic-clonic seizure. During her first evaluation at our clinic, we detected SWAS on the sleep video-EEG recording, which disappeared under corticosteroid treatment combined with AED therapy (Figure 4).

Because her cognitive impairment had been observed since she was 6 years old, after 3 years of AED treatment, we believed that the SWAS might also be an adverse reaction to antiepileptic medication and decided to progressively reduce the doses of clobazam.

It is, however, difficult to estimate the onset of EE-SWAS since the child did not undergo a sleep EEG as part of her routine electrophysiological evaluation in the beginning. The modification of both her AED regimen and SWAS improved her cognitive status as evidenced by a series of psychological evaluations using the WISC-IV evaluation scale.

The initial 1.5 Tesla MRI missed the diagnosis of hemimegalencephaly, which was later confirmed by a 3T MRI and added a new feature to a complex clinical picture and raised the suspicion of a mixed etiology – structural and genetic – that prompted genetic testing via Whole Exome Sequencing.

CONCLUSIONS

We suspected that a genetic syndrome encompassing structural abnormalities of the brain, skull, and skin, cognitive impairment, and epileptic encephalopathy with SWAS. Genetic testing revealed a heterozygous VUS in the TRIO gene associated with autosomal dominant mental retardation type 44 (MRD44).

Taking into account the clinical and paraclinical aspects of our patient, we considered other types of genetic syndromes as well, characterized by facial, cranial, and cerebral malformations, seizures and intellectual disability such as Angelman syndrome, MECP2-related disorders or Pitt-Hopkins syndrome[18-26].

Our patient's phenotype presented different cerebral structural anomalies that mostly affected neural migration as well as features that indicated a history of perinatal brain injury – gliotic lesions of the periventricular white matter with ventriculomegaly as a result of glial retraction. She also presented dental anomalies that are consistent with the phenotype of TRIO mutations, but she did not present with abnormalities of the fingers or evident intellectual disability after SWAS remission and benzodiazepine withdrawal[11-14].

It is yet to be established whether the VUS mutation of the TRIO gene we identified might be classified as a pathogenic mutation with a specific phenotype that includes structural brain abnormalities, skin lesions and seizures, also consistent with a neurocutaneous syndrome, given the common embryological origin of the aforementioned structures.

Periodic neurological, psychiatric and psychological evaluations are necessary to monitor her status and most importantly, periodic EEG evaluations should be performed, considering that although she was seizure-free, her EEG revealed SWAS. Moreover, genetic testing of the family members is required.

Finally, we hypothesize that our patient presents an atypical phenotype of a VUS mutation of the TRIO gene characterized by epileptic encephalopathy with SWAS, hemimegalencephaly, cognitive impairment, abnormality of skin pigmentation and dental features which partly overlaps with TRIO pathogenic variants but might suggest a different genetic neurocutaneous syndrome altogether.

Compliance with ethics requirements: The authors declare no conflict of interest regarding this article. The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from all the patients included in the study.

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