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Triple pathology in a patient with uncontrolled epilepsy: a case report

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Abstract

Background Sturge–Weber syndrome is an uncommon neurocutaneous disorder with characteristic vascular lesions, leptomeningeal angiomas, and facial nevi. Seizureis the most prevalent neurological sign of Sturge–Weber syndrome and complications related to seizure control, comorbidities, or outcome can make the way of medical care turbid. Accordingly, the co-occurrence of Sturge–Weber syndrome with mesial temporal lobe sclerosis/mesial temporal sclerosis and low-grade glioma has not been reported in literature.

Case report In this report, we present a 29-year-old Kurdish male with Sturge–Weber syndrome showing evidence of sclerotic changes in the medial part of the right temporal including the hippocampus in magnetic resonance imaging, in addition to a low-grade glioma. He used to have seizures, starting with left dominant somatosensory aura, before puberty. Interestingly, the semiology has changed to an epigastric aura afterward. Therefore, we assumed that there could be a new seizure onset zone. Seizures from the right mesial temporal region were recorded during long-term electroencephalogram monitoring admission. This finding was compatible with lesions found in the right temporal lobe.

Conclusion Debates arise whether the co-occurrence of mesial temporal sclerosis and low-grade glioma with Sturge–Weber syndrome lesions is incidental or secondary to Sturge–Weber syndrome pathogenesis. Furthermore, this association can be attributed to a common genetic underlying. While there is no compelling evidence in this case to address the exact pathogenicity, the impact of early diagnosis and intense control of primary seizures on preventing downstream effects, such as sclerosis and tumor formations, is considerable. We strongly believe further research is needed to address this concern.

Keywords Epilepsy, Sturge–Weber syndrome, Low-grade glioma, Mesial temporal lobe sclerosis, Case report, Mesial temporal lobe epilepsy, Hippocampal sclerosis

Introduction

Encountering a child who presents both seizures and forehead cutaneous angiomas, also known as port wine nevus, can greatly increase the likelihood of diagnosing Sturge–Weber syndrome (SWS), a nonhereditary syndrome [1]. This sporadic neurocutaneous disorder with a prevalence of 1 in 20,000–50,000 births can involve the eyes, scalp, face, and sometimes the neck or extremities and, moreover, the brain [2]. Abnormal vasculature, the main cause of this disease, is associated with somatic mutations in genes, such as *GNAQ*, located on

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chromosome 9 [3]. While cutaneous capillary-venous malformations are presented in over 90% of patients with SWS in certain studies [4], diagnosis confirmation depends on brain magnetic resonance imaging (MRI) with gadolinium contrast, encompassing calcification, leptomeningeal enhancement, and expansion of cerebral structures [5]. The crucial clinical feature of SWS is seizure. The prevalence of seizure among patients with SWS is over 70% and it manifests in ~ 75% of affected patients in the first year of life. Learning disorders, headaches, and stroke-like episodes are other manifestations of this syndrome [6]. Chronic lack of oxygen in cortical and subcortical brain tissue, caused by leptomeningeal vasculature malformation, is responsible for neurological pathogenesis, such as astrogliosis, calcification, sclerosis, cortex development defect, loss of the neurons, and atrophy [7]. In our case, the seizure semiology alternation since early adolescence and the MRI findings indicated that the patient was dealing with more than a typical SWS. Therefore, we conducted further detailed investigations, including long-term video electroencephalography monitoring (LTM). Furthermore, the coexistence of SWS, low-grade glioma (LGG), and hippocampal sclerosis has not been reported in literature, hence more research into this co-occurrence is necessary.

Case report

A 29-year-old right-handed Kurdish male was diagnosed with Sturge–Weber syndrome (SWS) and poorly controlled epilepsy since infancy. Since birth, significant hemangioma formations have been obvious on the right side of his face. At 11 months of age, following hospitalization for two circumcision and hernia surgeries, the first generalized seizure occurred. Since the first episode, he has been treated with phenobarbital escalating to a total dosage of 250 mg daily. During his teenage years and beyond, the frequency of his seizures decreased to twice a month. He also acknowledged that the clinical presentations of his seizures have changed since the age of 15–16 years. Witnesses reported that the majority of the former seizures began with left-sided paresthesia, without marching and convulsions, followed by loss of consciousness, with hand automatism and then left versive. He said irrelevant words in some of these attacks and occasionally had left-side Todd's paresis. The second seizure type has appeared since the patient's adolescence, starting as an epigastric aura, followed by impaired awareness and hand automatism. He had no recollection of his episodes after the auras. While these two types of auras have never occurred at the same time, second-type seizures have accounted for the majority of his seizures in recent years.

The physical and neurological examinations did not reveal any significant positive findings, nor did the patient have a positive family history of SWS or epilepsy. He had no history of tobacco, alcohol, or cigarette smoking. He and his parents were not evaluated for genetic disorders. Prior evaluations, including complete blood count (CBC) and metabolic panel, were normal. Neuropsychological tests showed that his overall intellectual function and verbal and performance IQ are reduced on average. Regarding memory function, his verbal memory was better than his visual memory. He had average performance on working memory, visuospatial, and executive functions.

Brain MRI with contrast and epilepsy protocol demonstrated tumor signals in the right temporal lobe's ventral dimension of the para-hippocampus gyrus with right mesial temporal lobe sclerosis and SWS vascular lesions. Atrophy and high signal intensity in the right hippocampus with obliteration of hippocampus head digitation showed shrinkage of this area with sclerotic changes versus the left side (mesial temporal sclerosis; MTS) (Fig. 1A).

A 9 × 10 mm high signal heterogeneous lesion with an intercortical cystic component (Fig. 1) without post-contrast enhancement, in the ventral aspect of the right Parahippocampal gyrus was also shown, suggesting a low-grade glioma (LGG). Atrophy of the right parietal lobe compared to the left side with cortical atrophy and sulci dilation was also noted. Prominent leptomeningeal enhancement in the right parietal lobe (Fig. 2), secondary atrophy with mild enlargement of the ipsilateral choroid plexus, and dilation of parenchymal veins, in favor of SWS [8], were seen.

Long-term video-electroencephalography monitoring (LTM)

7 days after medication withdrawal, one of his typical seizures was captured. The patient was asleep when the seizure started. Then he developed grimacing, followed by staring and impaired awareness. Afterward, he started left-hand automatism. The whole event took ~ 120 seconds without post-ictal Todd's paresis. The electroencephalographic ictal pattern started about 10 seconds before the clinical manifestations of the seizure, appearing as right anterior temporal 4 –5 Hz rhythmic theta (Fig. 3), and spreading to the left temporal regions occurred after ~ 10 seconds. There was postictal right temporal delta slowing. The patient developed bradycardia during the seizure, which continued afterward. Thus, we ended medication withdrawal and stopped further seizure evaluation Interictally, independent right anterior temporal epileptiform discharges were recorded. Although previous electroencephalographic studies are not available, we think that our patient has developed temporal lobe epilepsy in recent years on the

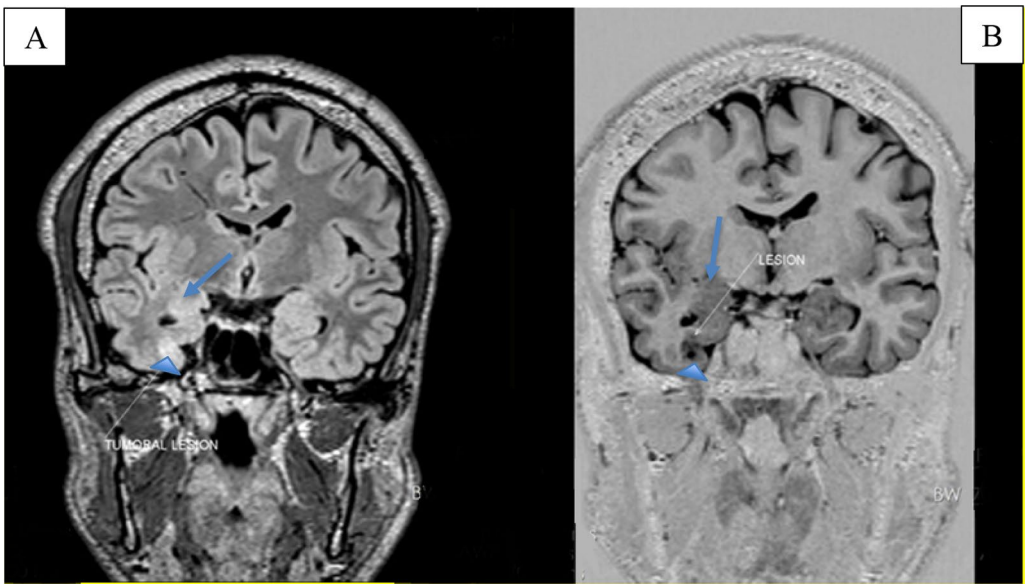

Fig. 1 **A**, **B** Brain magnetic resonance imaging coronal views show typical findings of hippocampal sclerosis on right as hippocampal atrophy (**A**, **B**) and increased Flair signal (**A**-arrow) and a heterogeneous lesion on the right parahyppocampal gyrus suggesting low-grade glioma as increased Flair signal (**A**-arrow head) with an intracranial cystic component (**B**-arrow head)

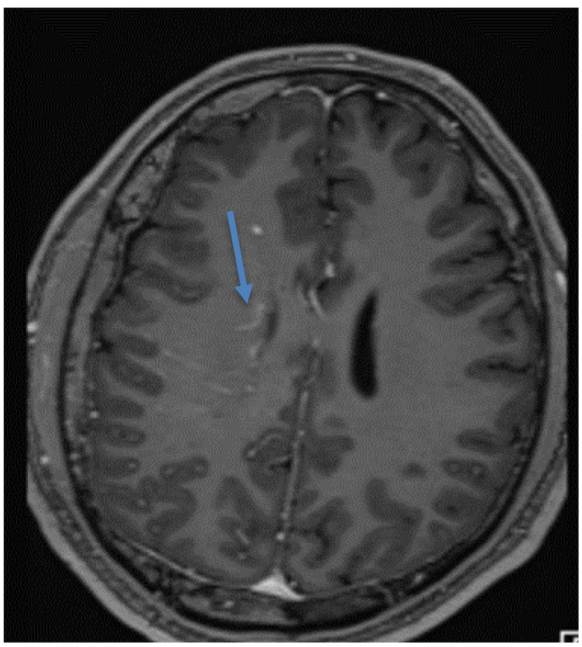

Fig. 2 Brain magnetic resonance image, axial T1-weighted with contrast sequences shows atrophy of the right parietal lobe with leptomeningeal enhancement (arrow) suggesting Sturge–Weber syndrome

basis of expressed seizure-semiology including oro-alimentary symptoms and abdominal-visceral sensations.

Phenobarbital was deemed not to be the most appropriate medication for the type of seizures, so it was gradually reduced to 100 mg daily, and 2000 mg daily of levetiracetam was added. In follow-up visits, we carefully monitored the adverse effects of the drugs and seizure manifestations. Despite the frequency of his seizures and drowsiness having decreased to half, the patient noted that his irritability and aggressiveness increased. No suicidal warning is documented. After discussing the pros and cons of surgical treatment with the patient, he developed a positive attitude toward that. Especially because it could allow him to reduce the medications he requires and to improve seizure control. Therefore, we have planned a fluorodeoxyglucose positron emission tomography (FDG-PET) scan to localize the epileptogenic zone more precisely, before scheduling him for surgery. The patient's treatment was disrupted as a result of the need to obtain the essential funds for the PET scan and surgical operation.

Discussion

A case of poorly-controlled epilepsy with LGG, SWS, and MTS considered a triple pathology, an unusual situation, has been reported. Triple pathology was applied to the coexistence and pathogenesis of three principal lesions in the brain through recent decades. Samura *et al.* [9] referred to the term epilepsy-related conditions for the first time in 2009 by reporting a case of hippocampal sclerosis (HS), cortical dysplasia (CD), and cavernous angioma (CA). In 2010, Maciunas and Associates [10] reported a comparable instance during their examination of surgical cases at the University

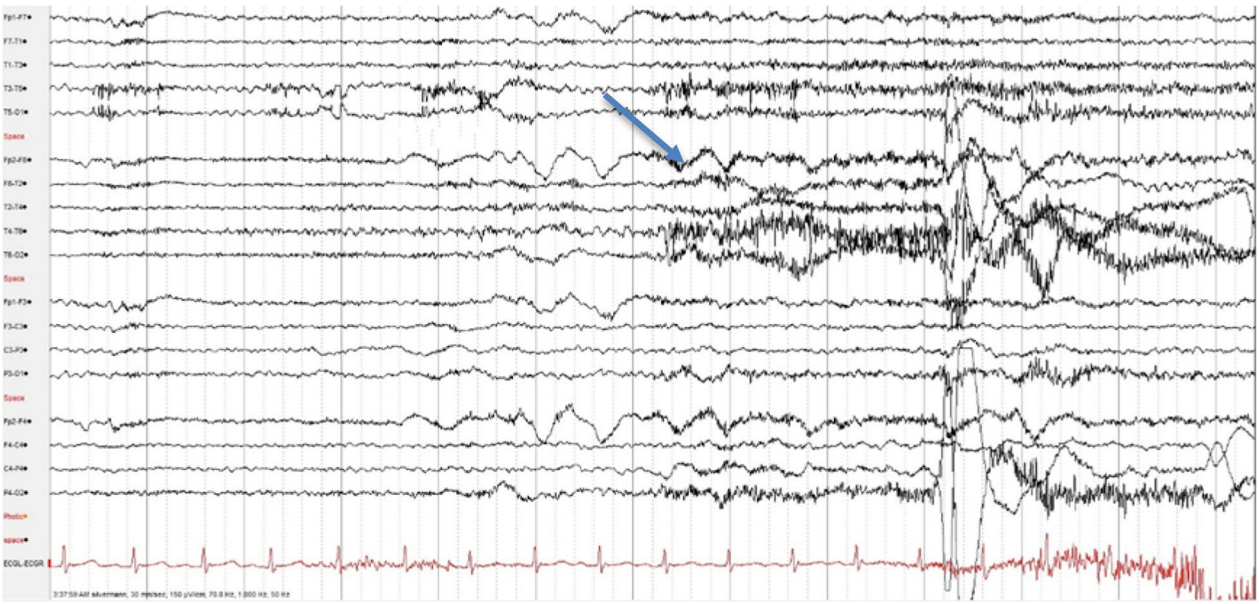

Fig. 3 The double banana montage of the electroencephalogram: electroencephalographic onset of seizure as right anterior temporal 4–5 HZ rhythmic theta (arrow)

Hospitals Case Medical Center, covering the period from 2003 to 2008. Yang *et al.* [11] reviewed literature alongside adding an HS, CD, and glioma case of epilepsy in March 2013. Accordingly, they postulated two possible explanations: similar pathological origin and a mixture of progression and occasionality. Then, 2 years later, Prayson *et al.* [12] found another two cases of HS, CD, and glioma in a review of their surgical cases in Cleveland from 2000 to 2012. While SWS is not known for an exact tumor formation underlying, the co-development of LGG and SWS has been previously reported [13, 14, 24]. As a common SWS feature, CD is found in more than 70% of patients, statistically similar to seizure [20]. It is also considered the common reason for intractable epilepsy [21]. A new study reports the accompaniment of SWS and HS, which can result in intractable epilepsy or can be a consequence of it [22]. In the same line, cavernous angiomas, such as vascular malformations, have been associated with CD frequently [18, 19] and drug-resistant epileptogenicity of them has been also indicated , especially in temporal lobe lesions [23]. Therefore, it is not clear whether or not all of these revealed lesions are causing seizures. On the other hand, as funding issues delayed treatment progress, a definitive pathological diagnosis has not been established yet. Furthermore, because of the limitations of the 10–20 recording system and capturing just one seizure of the patient, in addition to the unavailability of past electroencephalograms, we could not definitively determine the origin(s) of all his seizures.

Conclusion

As the seizures' semiology has changed significantly from left-sided somatosensory auras to epigastric auras in most of the episodes in this case, considering the results of neuropsychiatric tests and the capability of poorly controlled epilepsy to cause histopathologic defects, such as neuronal death and sclerosis, especially in the mesial temporal region [16], we hypothesized that seizure origin may have changed to right mesial temporal. While the dilemma of independent pathological origins for all three lesions and/or a combination of pathological progression is yet a matter of debate, the appropriate answer—similar to the reciprocal causal relationship of HS and epilepsy [17]—may lie somewhere in between. Finally, the significance of these issues is underscored. Besides, lowering the quality of life among uncontrolled epilepsy patients, the presence of mutations, such as *GNAQ*, indicates a predisposition to cancerous alterations in patients diagnosed with Sturge–Weber syndrome (SWS) [15]. Despite studies showing immediate intervention suggestions for better results in epilepsy remission [25], we believe that further research needs to be done on the concept of how effective seizure control in SWS-diagnosed children could prevent lobar sclerosis, CD, tumor formations, and cavernous angioma. Additionally, if there are any common genetic and pathophysiological origins for such triple pathology situations.

Abbreviations

SWS	Sturge–Weber syndrome
LGG	Low-grade glioma

MTLS	Mesial temporal lobe sclerosis
MTS	Mesial temporal sclerosis
HS	Hippocampal sclerosis
MRI	Magnetic resonance imaging
LTM	Long-term electroencephalogram monitoring
CBC	Complete blood count
MTLE	Mesial temporal lobe epilepsy
MG	Milligrams

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Author contributions
According to the CRediT (Contributor Roles Taxonomy) guidelines: 1. Conceptualization: *Aidin Taghilou*. 2. Data curation: *Melika Javani, Behnam Akbari, Hoda Naghshineh* 3. Formal analysis: *Abbas Tafakhori, Sara Ranji.* 4. Investigation: *Behnam Akbari, Melika Javani.* 5. Methodology: *Hoda Naghshine.* 6. Project administration: *Abbas Tafakhori*. 7. Resources: *Behnam Akbari, Melika Javani.* 8. Software: Not applicable. 9. Supervision: Hoda Naghshineh, *Sara Ranji, Abbas Tafakhori.* 10. Validation: *Saeideh Salehizadeh.* 11. Visualization: *Aidin Taghilou*, *Behnam Akbari.* 12. Writing—original draft: *Behnam Akbari.* 13. Writing—review and editing: *Behnam Akbari, Melika Javani, Hoda Naghshine, Saeideh Salehizadeh.* All authors read and approved the final manuscript.

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Availability of data and materials
Raw data including video-EEG monitoring data and brain imaging are not publicly available to preserve the patient's privacy under our center data protection regulation. However, data requests can be made to sara.ranji64@gmail.com.

Declarations

Ethical approval and consent to participate
The Islamic Republic of Iran's national policy does not require ethical approval.

Consent for publications
Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Competing interests
The authors declare that they have no competing interests. Specifically, the authors have no financial, personal, or professional interests that could be construed to have influenced the paper. There are no patents, products in development, or marketed products to declare. This does not alter our adherence to all the journal's policies on sharing data and materials. The authors alone are responsible for the content and writing of the paper.

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