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Clinical Reasoning: An Interesting Case of Drug Resistant Epilepsy in a 61-Year-Old Man With Abnormal MRI Brain Findings and Management With Vagal Nerve Stimulator

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Abstract:

A 66-year-old man with seizures that started at 61 years eventually developed drug-resistant epilepsy and was managed with medications and vagal nerve stimulation. The patient had a convulsive event at age 61, followed by recurrent events of confusion and speech arrest lasting 30-120 seconds. He underwent gadolinium enhanced MRI brain and angiogram which revealed pial enhancement in the right occipital, parietal, and posterior temporal regions with subcortical atrophy. CSF findings were unremarkable. Continuous video EEG showed electroclinical correlation for his episodes of confusion and speech arrest with recurrent brief runs of rhythmic delta from the right temporal region with evolution and spread to the entire right hemisphere. The patient tried multiple antiseizure medications including valproic acid, topiramate, phenytoin, carbamazepine, levetiracetam, brivaracetam, lamotrigine without success. He was eventually put on a combination of lacosamide, zonisamide, clonazepam, and primidone, which helped to certain extent, but the patient continued to have daily episodes and 10-12 electroclinical seizures noted on a follow-up 24-hour ambulatory EEG. Follow-up MRI brain with contrast confirmed the diagnosis. Phase II intracranial monitoring for surgical management was offered to the patient which he deferred due to risks. Vagal nerve stimulator (VNS) was also offered as a palliative therapy to which the patient agreed. Gradual titration of VNS settings over 1 year helped to achieve seizure freedom. Presentation of focal seizure with this type of atypical etiology is rare. Typically surgical management is used to achieve seizure freedom in this condition; successful management with VNS has not been reported so far.

Section 1

A 66-year-old left-handed man initially presented to neurology clinic for evaluation and management of intractable seizures. His first seizure was described as a generalized convulsive seizure at the age of 61. Following this, he started experiencing recurrent episodes of feeling “spacy” and confused with speech

arrest. These episodes would last for about 30 seconds to 2 minutes, almost every day according to his family especially with stress or tiredness. These episodes compromised his daily routine with impairment in his ability to give speeches at church. Neurological examination was normal except mild executive dysfunction noted but intact short and long-term memory. His neurological exam including cranial nerves, sensorimotor, coordination, gait and reflexes was normal. Skin examination was normal. He had CT head and MRI brain with and without contrast showed leptomeningeal/pial enhancement involving the right occipital, inferior parietal, and posterior temporal lobes with associated volume loss (Figure 1, A–D). These findings were unchanged when compared with previous 5 annual MRIs. He also had routine EEG and CSF analysis which were unremarkable. MR angiography confirmed the MRI brain findings with evidence of leptomeningeal angiomatosis, no aneurysm or arteriovenous malformation.

Questions:

1. What is the diagnosis based on the clinical features and investigations?
2. What are the common features and timeline for the diagnosis of this condition?
3. How frequently do patients experience epilepsy with this condition and what is the expected outcome?

Section 2

The aforementioned MRI and MRA findings were suggestive of a rare variant of type III Sturge-weber syndrome with isolated pial angiomatosis. Sturge-weber syndrome (SWS) is a neurocutaneous syndrome with typical triad of port wine facial nevus in trigeminal distribution, leptomeningeal angiomatosis ipsilateral to the facial nevus and glaucoma.[2] The incidence of this condition is 1 in 5000 live-births. SWS is further classified as type I with typical triad, type II when facial angioma is present without CNS involvement, and Type III with exclusive leptomeningeal angioma with absent cutaneous findings.[2] Diagnosis of type III SWS requires MRI brain and MR angiogram with and without contrast.

Physicians must have a high index of clinical suspicion.[11] Common symptoms are seizures (75-90%), intellectual disability and developmental delay (50-75%), hemiplegia (40-45%), headache (40-60%), glaucoma (30-70%), hemianopsia (40-45%), and hemiparesis (25-60%). [10, 11] It is commonly diagnosed in neonates and rarely found later in life. There are only few case reports describing the diagnosis of this syndrome in the 5th and 6th decade of life[9] Patients with seizure freedom more than 6 months at a time are considered to have a good seizure control, which is noted in 60-70% of patients with anti-seizure medications.[3]

Questions:

1. What are the options for the patient with drug-resistant nature of epilepsy with this condition?
2. What should be the ideal time for referring patients to the epileptologist for further work up?

Section 3

Patients who continue to have frequent seizures (typically more than once a month) despite treatment with ≥2 well tolerated and adequately dosed antiseizure medications are considered to have drug-resistant epilepsy. These patients require further evaluation by an epileptologist and possibly an admission to epilepsy monitoring unit. Amongst the use of antiseizure medications, carbamazepine and oxcarbazepine are usually the first choice. Topiramate and levetiracetam are good choices for second agents.[3] Patients with drug-resistant epilepsy in SWS have undergone surgical options like lobectomy, hemispherectomy, and corpus callosotomy.[10, 11] Patients who undergo early surgery have the potential to achieve seizure freedom and significant reduction postoperatively. [10] Presurgical work up requires neuropsychology assessment for memory evaluation and language lateralization. Patients with drug-resistant epilepsy benefit from further discussions at a comprehensive epilepsy conference to seek opinion from different providers including neuroradiologist, neuropsychologist as well as the neurosurgeon.

Questions:

1. What happened to this patient?
2. Why was the VNS considered in our patient?

Section 4

Our patient tried multiple antiseizure medications including valproic acid (caused weight gain and poor efficacy after 4 months), topiramate (cognitive side effects after 3 weeks), phenytoin and carbamazepine (not effective despite of optimal titration at the end of 2 months), levetiracetam (mood problems in 1 month), brivaracetam (mood problems in 2 months) and lamotrigine (intolerance after 4 weeks), but had no success in achieving acceptable seizure control. Our patient was referred to an epileptologist who suggested admission to the epilepsy monitoring unit. The patient had 2-day video EEG monitoring which captured over 20 brief focal electroclinical seizures characterized by rhythmic 2-3 Hz delta frequency activity arising from the right temporal region (F8-T4 derivations) with evolution into higher amplitude rhythmic delta along with spread to involve the entire right hemisphere prior to abrupt cessation (Figure 2, A–C). These episodes were associated with speech arrest, paraphasic errors and confusion noted on exam. As he had failed multiple antiseizure medications, he was discharged on a combination of lacosamide, zonisamide, clonazepam and primidone. Primidone was mainly used for his essential tremors but also has weak antiseizure activity. The patient had a follow-up 24-hour ambulatory EEG after 2 months, which captured 10-12 brief focal electro-clinical and electrographic seizures and he was unaware of majority of the events, but the family identified speech arrest during few of these events. He was offered presurgical work up which included neuropsychological assessment. This concluded minimal deficits in language and executive functioning but overall intact short and long-term memory. He did not have any motor deficits except average performance in grip strength on his nondominant (right) hand. The patient was offered phase II intracranial EEG monitoring using stereo-

EEG; however, given the extent of right hemispheric lesion (pial angiomatosis) and well preserved neurological function as well as the potential risks associated with intracranial surgery (e.g., vision deficits, weakness, sensory impairment, infection, etc.), he opted against epilepsy surgery. His case was discussed in the epilepsy surgical conference and a decision was made to proceed with a palliative option of vagal nerve stimulator (VNS, Sentiva 1000) implantation. The patient was explained about potential complications of VNS implantation (e.g., infection, vagal nerve injury, vocal cord paralysis, bradycardia, voice changes, headache and paresthesia). He was gradually up titrated on the VNS settings over a period of 12-16 weeks and was maintained on output current 2.5 mA, signal frequency 30 Hz, pulse width 250 microseconds, on time 30 seconds, off time 5 mins, magnet current 2.75 mA with pulse width 500 microseconds and duration of 60 seconds; he was continued on medical management along with that as well. The patient achieved good seizure freedom after 9-12 months follow up and did not have any clinical seizure reported by himself or family. A follow up 24-hour ambulatory EEG at 1 year and 2 years interval showed brief runs of intermittent focal right hemispheric slowing without significant evolution or clinical manifestations.

Discussion

Sturge-weber syndrome is diagnosed early in neonatal age when patients have port wine facial nevus or when patients present with seizures or headaches and abnormality noted on MRI brain. It is very rare to be seen in later life. [2,9,10] It is thought to be caused by abnormal persistence of embryonic venous plexus in close proximity to ectoderm that was destined to form venous drainage of occipital and parietal region of brain as well as facial skin.[7,10] The low flow angiomata in Sturge-weber syndrome are at risk of thrombosis and calcification which eventually leads to ischemia and gliosis of surrounding nervous tissue and atrophy. [2,8] These patients can benefit from daily aspirin to prevent thrombosis in low flow angioma. The majority of the cases are diagnosed before age 12.[11]

Our patient is unique as he had type III Sturge-weber syndrome with isolated pial angiomatosis diagnosed in his 6th decade. To our knowledge, there are few cases reported that have been diagnosed at a later age.[9] MRI brain without contrast may not show leptomeningeal angioma at times and contrast imaging is very important in patients suffering from seizures to achieve a good diagnosis.[9] Cerebral calcifications can be seen on MRI brain in patients with encephalitis, purulent meningitis, celiac disease, leukemia and ossifying meningoencephalopathy, and hence appropriate investigations including CSF analysis and a cerebral angiography are advised. [2,8] With this syndrome, 75-90% of the patients may suffer from epilepsy; diagnosis of type III SWS requires high index of suspicion.[8,10,11] The late diagnosis and poor control of seizures may lead to surrounding atrophy as well as cognitive decline in patients.[3,10] Patients with ≤2 seizures in a 6-month duration are considered to have a good seizure control.[3] Patients with seizures which are resistant to ≥2 antiseizure medications should be referred to an epileptologist and should be admitted to epilepsy monitoring unit for better characterization of seizures and medication optimization. When the seizures remain drug-resistant, patients should be offered surgical options and appropriate investigations to assess for surgical candidacy.[10,11] To this date, several surgical options like lobectomy and hemispherectomy, as well as palliative corpus callosotomy have been used and proven to be beneficial.[10,11] VNS is a palliative option reserved for patients with drug-resistant epilepsy for whom epilepsy surgery is not feasible. To our knowledge, use of VNS for the successful management of drug-resistant focal seizures in a patient with Sturge-weber syndrome has not been reported yet.[3,4,10]

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Figure 1. MRI and CT Images. (a) Contrast enhanced T1 gadolinium image shows enhancement of vascular structure in right occipital, parietal region, leptomeningeal angioma. (b) Susceptibility weighted images shows presence of blood within leptomeningeal angioma in the same region. (c) CT Head image shows calcification in the right occipital and parietal region, surrounding the leptomeningeal angioma. (d) Sagittal contrast enhanced MRI image shows presence of leptomeningeal angioma, in right parietal and occipital region, extending to posterior temporal region as well.

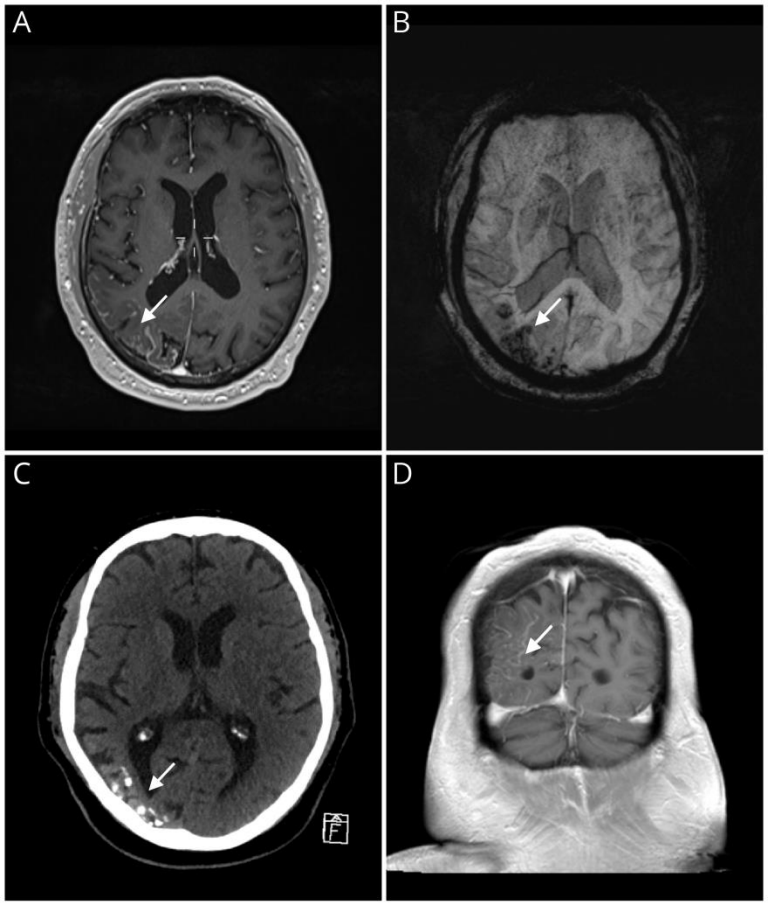
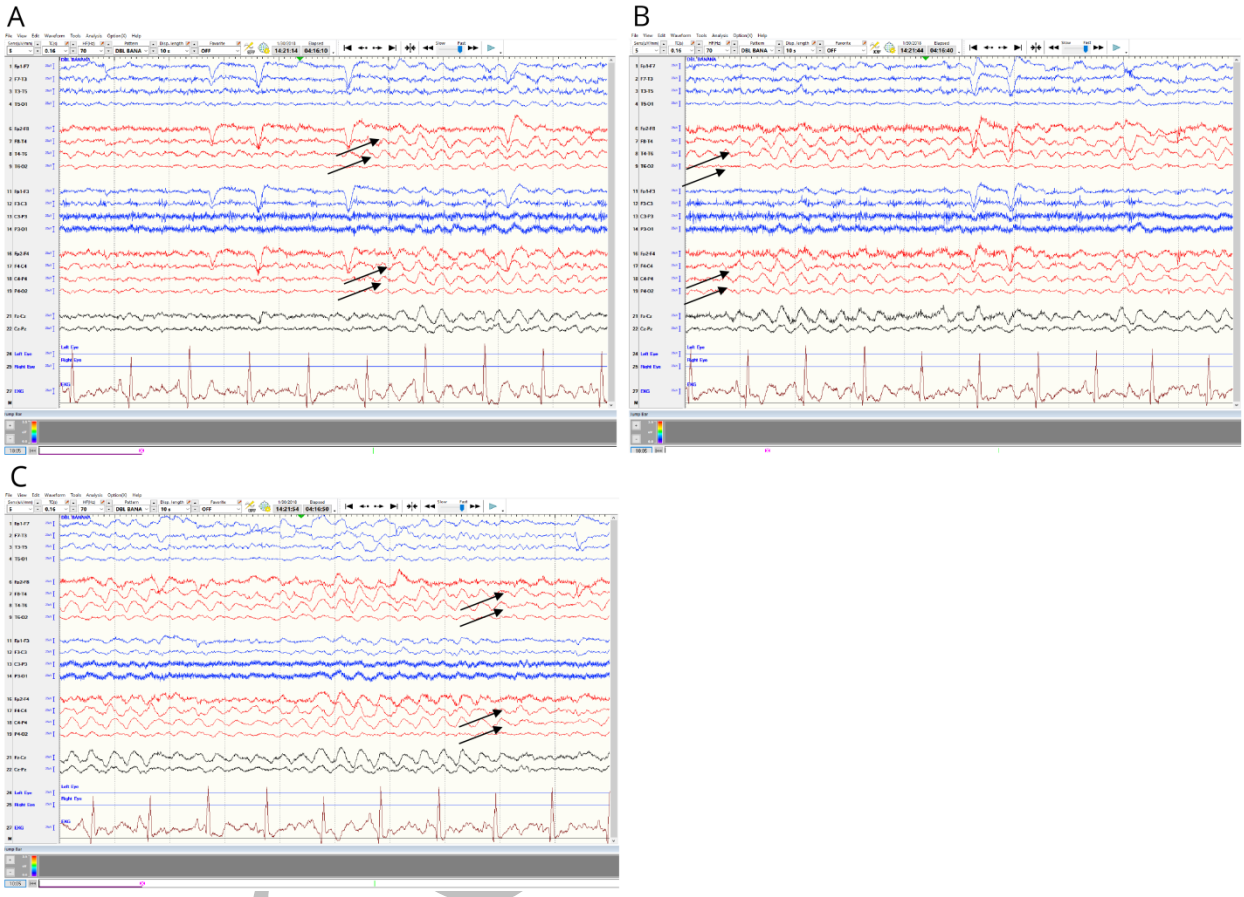


Figure 2 EEG images: (a) shows onset of low amplitude rhythmic delta activity over the right temporal region (b) shows evolution to higher amplitude rhythmic delta involving the entire right hemisphere (c) abrupt cessation of ictal rhythm



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