Clinical Reasoning: A 56-Year-Old Man With Unusual Presentation of Subacute Encephalopathy and Seizure

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Section 1

A 56-year-old, right-handed man presented with subacute confusion and seizures following a recent stroke. The ischemic event occurred in the left medial temporal region, resulting in right-sided hemiparesis, dysphagia, and dysarthria. The patient's family noticed cognitive decline after the stroke, including difficulties with reading, spelling, and recognizing faces. The stroke workup revealed elevated low-density lipoproteins (200) and hemoglobin A1c (6.5), as well as a normal echocardiogram. A treatment of aspirin and atorvastatin was started. The first seizure, which occurred 1 month after the stroke, also prompted the use of levetiracetam (500 mg) twice a day. This treatment proved effective until the day of admission, when the patient presented with multiple episodes of focal motor to bilateral tonic-clonic seizure, persisting more than 5 minutes, and convulsive status epilepticus. He received lorazepam, which successfully resolved the episodes.

Vital signs were normal. However, on examination, the patient appeared unable to follow commands. No asterixis, meningismus, or nuchal rigidity was evident, brainstem reflexes were active, and he could localize to noxious stimuli in all extremities. In addition, deep tendon reflexes measured at 2+ throughout and Babinski signs were absent bilaterally.

Questions for Consideration:

1. What is the differential diagnosis and workup for subacute confusion and recurrent seizure?
2. What are the initial steps in evaluation?

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Section 2

The differential diagnoses for subacute confusion and recurrent seizure are as follows:

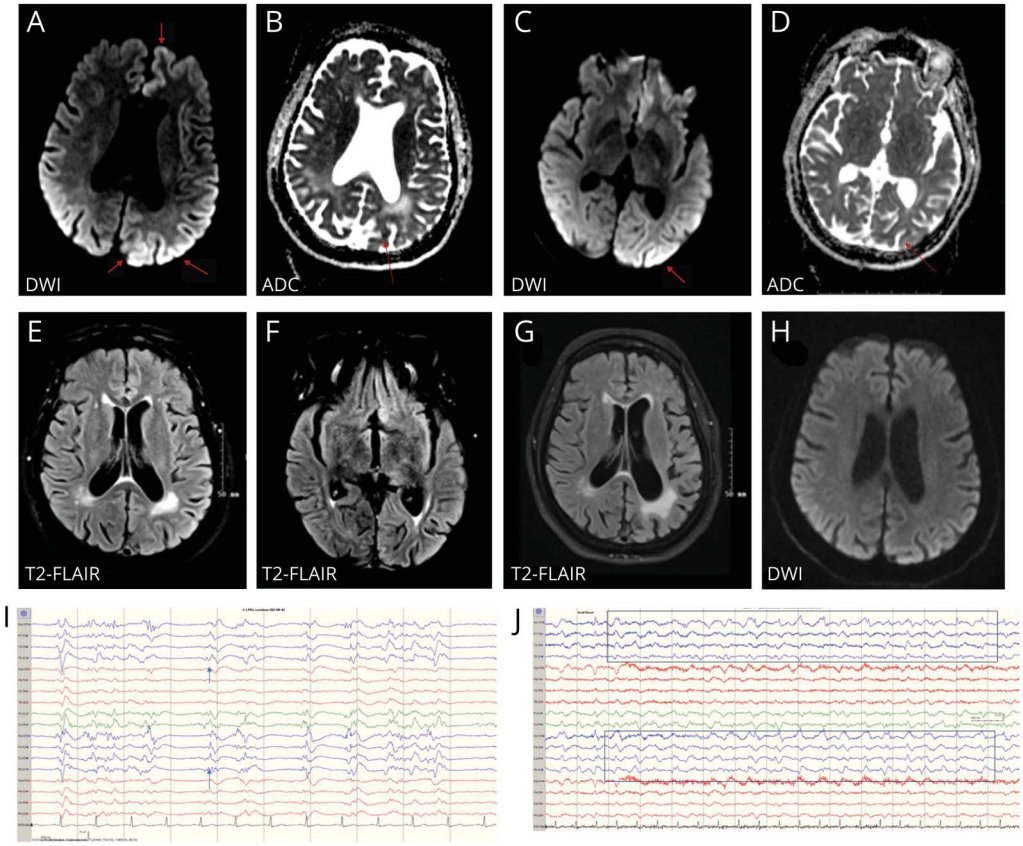
a. Vascular: Recurrent stroke can present as a seizure and cognitive decline.
b. Epilepsy: Recurrent seizure from poststroke epilepsy, including nonconvulsive status epilepticus, could produce the changes described.
c. Infection: Meningitis or encephalitis is a possibility, as herpes virus and enteroviruses can present with similar symptoms. Given the lack of meningismus or fever, these infections may be less likely.
d. Toxic and metabolic disorder: No recent exposure to toxins or new drugs was reported, and the patient did not have prior history of brain trauma or anoxic brain injury. However, systematic infection, nutritional deficiency, and metabolic derangement should be investigated.
e. Noninfectious inflammatory condition: Demyelinating disorders such as MS, autoimmune encephalitis (AE), and other inflammatory conditions including sarcoidosis or systemic lupus erythematosus could be investigated on further workup.
f. Rapidly progressive dementia: Prion disease, including Creutzfeldt-Jakob disease (CJD), can include similar symptoms

Brain MRI and continuous EEG (cEEG) were obtained based on the above differential diagnoses. The brain MRI showed cortical ribboning in diffusion-weighted imaging (DWI), correlating with faintly apparent diffusion coefficient (ADC) signals (Figure 1, A–D) and FLAIR hyperintensities in the left occipitoparietal and inferomedial frontal cortex, with no abnormal contrast enhancement (Figure 1, E and F). The 24-hour cEEG showed frequent left-sided lateralized periodic discharges (LPDs), with 1 focal electrographic seizure arising from the left hemisphere (Figure 1, I and J). As a result, levetiracetam was increased to 1000 mg twice a day—no further seizures appeared on cEEG.

Questions for Consideration:

1. What is the differential diagnosis now based on the MRI and EEG findings?
2. What are the next steps of evaluation?

Figure 1 Serial Brain MRI Result and cEEG Finding



(A–F) MRI findings at initial presentation showed cortical restricted diffusion (cortical ribboning) with mild ADC signals in the left parieto-occipital and inferomedial frontal regions (arrows) (A–D) and associated FLAIR hyperintensities (E and F). (G and H) Interval resolution of the FLAIR hyperintensities (G) and cortical restriction diffusion (H) and in the left parieto-occipital and frontal regions. (I) Initial EEG showed lateralizing periodic discharges in the left hemisphere (arrow). (J) One focal electrographic seizure arising from the left hemisphere in the continuous EEG (in square shape). ADC = apparent diffusion coefficient; FLAIR = fluid-attenuated inversion recovery.

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Section 3

The above MRI findings can be seen in sequalae of status epilepticus, infectious or AE, and CJD. Given the nonvascular distribution of MRI abnormalities, a stroke diagnosis was unlikely. LPDs are nonspecific and could be seen in all referenced etiologies. CSF studies were also obtained and showed a white blood cell count of 2 cells/μL, a glucose of 47 mg/dL, and a protein of 46 mg/dL. The opening pressure measured at 10 cmH_2O. All CSF pathogen studies, including bacterial and fungal cultures, herpes simplex virus PCR, *Cryptococcus* antigen and PCR, Epstein-Barr virus PCR, enterovirus, West Nile virus, varicella, and Lyme disease, were negative. The cytopathology and flow cytometry showed no malignant cells. In addition, oligoclonal bands were absent in the CSF. Vitamin B12 level, thyroid function, ammonia, and other toxic-metabolic tests, such as blood and urine cultures or chest X-ray, were normal. Notably, the patient tested positive for the 14-3-3 protein, as well as elevated levels of T-tau protein at >4,000 mg in the CSF.

On the third day of admission, the patient remained encephalopathic, intermittently following 1-step commands. He was aphasic and developed decreased right-sided visual abilities, which suggested possible homonymous hemianopsia. Alternatively, all other cranial nerves were intact. The patient had poor coordination with intention tremors on attempts to reach for objects. He continued to have right-sided hemiparesis, which was present before admission, with brisker reflexes in the right limbs compared with the left.

Questions for Consideration:

1. Does this information suggest the probable diagnosis of CJD?
2. What else should be included in the differential diagnosis?

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Section 4

According to the sporadic CJD diagnostic criteria,[1] the patient's symptoms suggested a probable CJD diagnosis. In this case, rapidly progressive cognitive decline including homonymous hemianopsia, cerebellar signs of tremor and poor coordination, and pyramidal signs of hemiparesis and hyperreflexia, along with LPDs in the cEEG and cortical ribboning at 2 cortical regions in MRI aligned with these standards. Although a periodic discharge pattern, such as a LPD or positive sharp wave complex (PSWC), is a nonspecific EEG finding, it can be seen in up to two-thirds of sporadic CJD.[1]

On day 11 of hospitalization, the patient developed another seizure type, featuring frequent episodes of brief right face and arm dystonic jerking movements. Lacosamide was added to his treatment regimen, and another cEEG showed continuing PSWC in both the left and right hemispheres, without evolution to electrographic seizures. His examination remained unchanged.

Question for Consideration:

1. What is the clinical significance of this new seizure type?

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Section 5

The new form of seizure is a faciobrachial dystonic seizure, which is associated with AE—particularly, voltage-gated potassium channel complex antibody (LG1/contactin-associated protein 2 [CASPR2]) mediated encephalitis. According to a recent Antibody Prevalence in Epilepsy prediction model score for AE,[2] a high predictive value of antibody positivity was present in this patient due to the new-onset epilepsy, faciobrachial dystonic seizures, and MRI abnormalities.

An extensive serum and CSF antineuronal antibody panel was sent to Mayo Laboratories on day 20 of hospitalization and came back positive on day 35 for the anti-CASPR2 receptor IgG antibody in serum, using the cell-based immunofluorescence assay. The RT-QuIC in CSF returned negative. Meanwhile, given suspicion of possible AE, the patient received 1,000 mg daily of IV methylprednisolone for 5 days, from day 20 to day 24 of hospitalization.

Question for Consideration:

1. Does this information indicate the diagnosis of AE?
2. What treatment options can be offered?

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Section 6

Despite conflicting data, the occurrence of the faciobrachial dystonic seizure and positive antineuronal antibodies made the diagnosis of AE more likely. The initial course of treatment for AE consists of corticosteroid and IV immune globulin (IVIg) or plasmapheresis.[3] Corticosteroid alone is usually not enough to ameliorate the autoantibody-mediated immune process, so the addition of IVIg or plasmapheresis is often needed. In fact, plasmapheresis may have a more rapid onset in removing autoantibodies compared with corticosteroid alone.[3] The patient was started on plasmapheresis for 5 sessions. Another brain MRI was obtained 2 weeks after this treatment and showed improvement of signal abnormality in the medial left occipital lobe, as well as resolution of restricted diffusion (Figure 1, G and H). He started to show improvement in mental status 4 weeks after plasmapheresis.

As AE can be paraneoplastic, the patient also underwent cancer screening including a CT scan of his chest, abdomen, and pelvis, in addition to a testicular ultrasound. Neither of the scans showed evidence of malignancy. A treatment with rituximab every 6 months was prescribed. After the first dose of rituximab, the patient was discharged to a rehabilitation facility where he demonstrated continuous improvement. On day 150 of follow-up, he was awake and alert, with increased ability to use toiletry. He was able to shower and eat independently, without assistance. Visual fields were intact on evaluation. The patient could ambulate with a walker, with mild weakness on the right side. He remained seizure-free on levetiracetam and lacosamide.

Question for Consideration:

1. What are the major diagnostic challenges in this case?

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Section 7

Our case discusses the challenges of diagnosing AE with phenotypical similarities to CJD. A retrospective study of prion-negative brain autopsy cases facilitated by the US National Prion Disease Pathology Surveillance Center found that 8.5% had AE.[4]

Based on the diagnostic criteria,[1,2] this case raises concerns for both CJD and AE, especially when laboratory and imaging data provide confusing results. 14-3-3 and tau proteins are often ordered for CJD, but it may not sufficiently discriminate between CJD and other disorders, given its low sensitivity.[5] MRI with ADC/DWI sequences has a higher sensitivity (97%) than 14-3-3 and tau if there is cortical ribboning on different cortical regions.[6] The patient's MRI showed cortical ribboning in multiple areas, similar to reported findings in CJD. LPD in EEG, including PSWC, is also associated with CJD. One retrospective study of AE cases mimicking CJD showed that 13 of 17 presenting with PSWC had CJD, whereas none with AE had PSWC.[7] However, LPD including PSWC has been seen in AE in another study.[8] Recently, RT-QuIC emerged as a new marker to detect small amounts of abnormally folded prion proteins in CSF, with a greater sensitivity (92%) and specificity (98%) rating than either 14-3-3 or tau protein.[9]

Although the patient's presentation of cognitive decline, visual/cerebellar signs, and pyramidal signs, multiple laboratory findings, and imaging results showed phenotypes consistent with CJD, other clinical features including faciobrachial dystonic seizures, negative RT-QuIC, and immunotherapy response pointed toward AE. Notably, a recent case that is the opposite of our patient, which describes a postmortem diagnosis of CJD with a positive anti-CASPR2 antibody.[10] Thus, using any biomarker or diagnostic findings alone can lead to misdiagnosis. It is important to use phenotype-directed evaluations in correlation with laboratory findings when encountering a difficult case with conflicting data.

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