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Pearls & Oy-sters: Rapidly progressive dementia

Prions or immunomediated?

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PEARLS

- Voltage-gated potassium channel (VGKC) antibody–associated encephalitis is a well-known form of limbic encephalitis characterized by acute to subacute onset of confusion and cognitive impairment, mediotemporal seizures, and psychiatric disturbances.
- Among other causes of rapidly progressive dementia, this condition is responsive to immunotherapy, and therefore correct and early diagnosis is crucial.
- Sporadic Creutzfeldt-Jakob disease (sCJD) typically presents with rapidly progressive dementia associated with a mixture of cerebellar, extrapyramidal, visual, behavioral, or psychiatric symptoms.

OY-STERS

- VGKC antibody–associated encephalitis may be confused with sCJD due to overlapping of clinical, neuroradiologic, and biochemical features; careful and complete medical evaluation is imperative in order to prevent potential misdiagnosis of a reversible condition for a terminal one.

CASE REPORT A 65-year-old woman was admitted after a 4-month history of rapidly progressive cognitive impairment. Her medical history was unremarkable without history of cigarette smoking, alcohol abuse, or neurologic or psychiatric illness. She was able to perform all activities of daily living until 4 months prior to evaluation, when she developed unusual behavior and memory impairment. She also complained of malaise and fatigue. Two months prior to evaluation, she began to have difficulty with her daily activities, developed depression, and developed more severe behavioral and memory problems. She was seen by a psychiatrist and underwent a brain MRI, which did not demonstrate any abnormalities. By the time she presented for neurologic evaluation, she had developed confusion and was unable to take care of herself. Due to the rapid progression of symptoms, the patient was admitted for further investigation.

Neurologic examination demonstrated no cranial nerve or sensory deficits. There was no weakness present but the patient did have extensor plantar responses bilaterally. Mini-Mental State Examination score was 19/30 (temporal and spatial disorientation with verbal learning impairment) and extensive neuropsychological assessment confirmed impairment of language (verbal fluency and naming), memory, and selective attention. The patient was also found to have fluctuations of consciousness as well as hallucinations. EEG demonstrated a background pattern of 7–8 Hz and slow biphasic and triphasic waves with higher amplitude in frontal regions (figure, A). A few days after admission, the patient developed faciobrachial tonic seizures and generalized tonic-clonic seizures. The severity and frequency of seizures, as well as the EEG abnormalities (figure, B), improved after treatment with levetiracetam. Neuropsychological features, however, remained unchanged. Standard blood examinations were normal. Blood tests were also negative for lupus anticoagulant, antinuclear antibodies, antibodies to extractable nuclear antigens, antineutrophil cytoplasmic autoantibodies, anticardiolipin antibodies, and cryoglobulins. Serum neoplastic markers and angiotensin-converting enzyme were within normal range.

Fluid-attenuated inversion recovery (FLAIR), T2-weighted, and diffusion-weighted imaging (DWI) MRI revealed areas of hyperintense signal involving the right hippocampal cortex and left striatum (figure, C–E). Comparison with the apparent diffusion coefficient (ADC) map revealed restricted diffusion in the left caudate and putamen (figure, F). CSF cell count and total proteins were normal; isoelectric focusing showed oligoclonal bands in serum and CSF. Serum and CSF antibodies against *Borrelia burgdorferi* and *Treponema pallidum* and CSF culture for bacteria and fungi were negative. CSF and blood nPCR assays were negative for herpes simplex virus 1 and 2, cytomegalovirus, HIV, Epstein-Barr virus, human herpesvirus 6, varicella-zoster virus, parvovirus B19, measles virus, adenovirus, and enteroviruses.

CSF examination revealed a markedly increased total tau protein (>1,200 pg/mL) and a positive 14-3-3 protein test. The level of the latter was calculated

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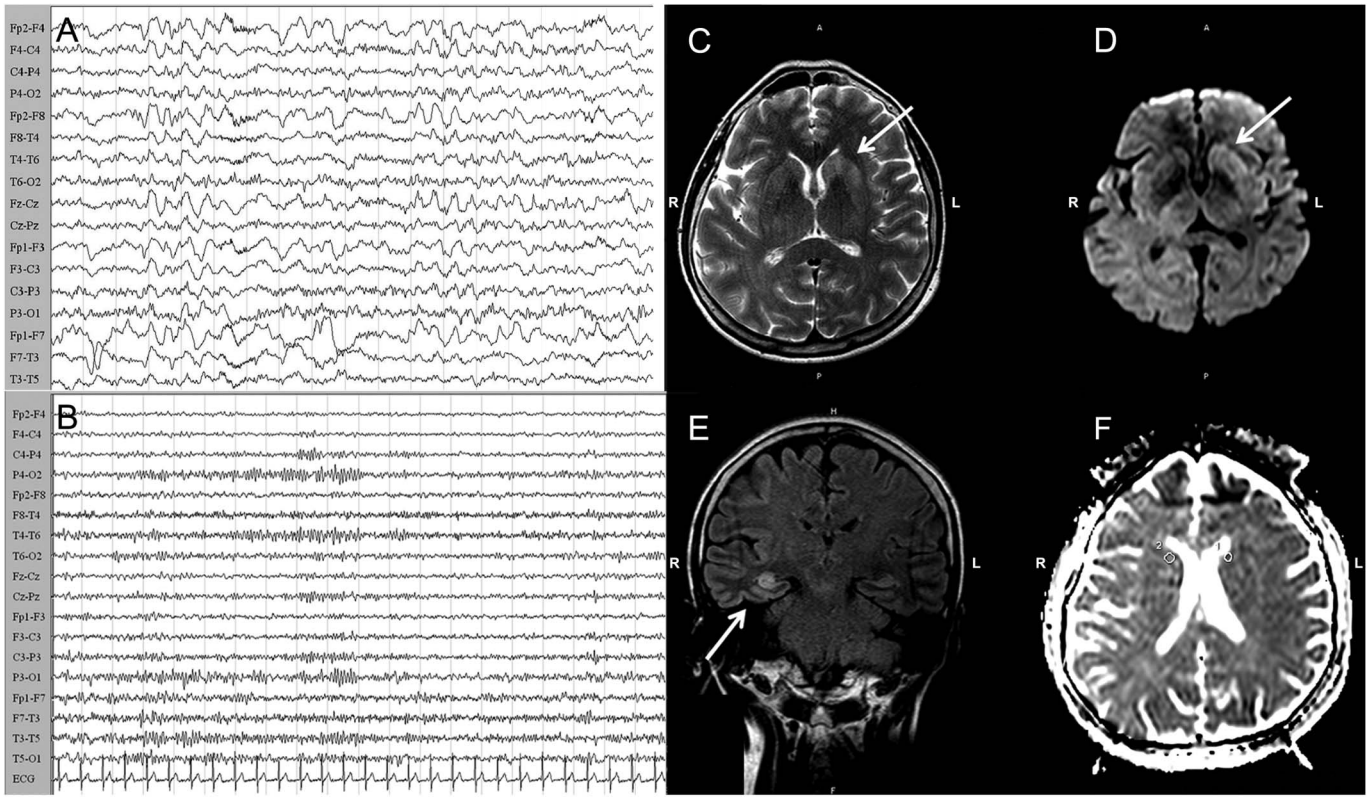
Figure EEG and MRI



EEG recordings show diffuse slowing with slow biphasic and triphasic waves with higher amplitude on frontal regions (A). EEG recording after oral treatment with levetiracetam shows the resolution of these waves (B). Brain MRI at admission: axial T2-weighted and diffusion-weighted imaging sequences demonstrate hyperintense areas involving the left striatum (C, D, arrow). Coronal FLAIR with hyperintensity of the right hippocampal cortex (E, arrow). Apparent diffusion coefficient map reveals normal diffusion coefficient in right caudate (F, circle 2) and restricted diffusion in left caudate and putamen (F, circle 1).

semiquantitatively by Western blotting, as described.[1] Densitometric value of the 14-3-3 band in the patient was 5-fold higher than that of the internal control sample (non-CJD subject who had trace levels of 14-3-3 protein) and comparable to that of a typical sCJD case with methionine homozygosity at codon 129 in the prion protein gene (*PRNP*) and pathologic prion protein type 1 (MM1 type) confirmed at autopsy. *PRNP* analysis revealed methionine/valine heterozygosity at the polymorphic codon 129. Total body CT imaging, esophagogastroduodenoscopy, colonoscopy, and gynecologic evaluation were normal.

IV immunoglobulin (0.4 mg/kg/d for 5 days) and steroids (methylprednisolone 1 g/d for 5 days) were administered, followed by a course of oral corticosteroids (50 mg/d oral prednisolone). Three weeks later, the patient's clinical condition began to improve and brain MRI showed partial resolution of the FLAIR, T2, and DWI hyperintensities in the right hippocampal cortex and left striatum. One month later, serologic evaluation revealed VGKC/leucine-rich glioma-inactivated 1 (LGI1) autoantibodies. Screening for other autoantibodies, including onconeural antibodies (Hu, Yo, Ri, CV2, amphiphysin, Ma2) and autoantibodies against neuronal surface antigens (AMPAR, NMDAR, CASPR2), was negative.

Three months after her initial presentation, a second cycle of IV immunoglobulin and steroids followed by oral corticosteroids was administered. The antiepileptic therapy was modified, with gradual introduction of lamotrigine (up to 200 mg/day) followed by discontinuation of levetiracetam. In the following months, the patient's condition continued to improve. There was a disappearance of seizures and a progressive recovery of memory function, confirmed by neuropsychological testing.

A repeat CSF assay performed 2 weeks after the second immunomodulatory therapy cycle revealed normal level of both 14-3-3 and total tau proteins. Four months later, brain MRI showed a further reduction of the hyperintense signals in all affected areas. At the most recent visit, 1 year after her initial presentation, the patient has remained seizure-free for 8 months, was oriented, and showed improved memory.

DISCUSSION Due to the rapidly progressive onset and course of cognitive and behavioral impairment, VGKC antibody–associated encephalitis may present similarly to sCJD.[2] sCJD, the most common human

prion disease, is a phenotypically heterogeneous disorder including at least 6 distinct subtypes, which are largely determined by genotype at the polymorphic codon 129 (encoding methionine or valine) in the *PRNP* and by the type (type 1 or type 2) of the abnormal prion protein accumulating in the brain.[3]

Due to the wide and often nonspecific clinical phenotype, the differential diagnosis between sCJD and other rapidly progressive dementias, including autoimmune encephalitis, mainly relies on neurophysiologic, imaging, and laboratory testing. Among them, EEG criteria have the lowest sensitivity and specificity, since the supportive diagnostic pattern (e.g., periodic 1–2 Hz triphasic sharp waves) develops in only about two-thirds of sCJD cases and can be seen in a variety of other diseases (e.g., toxic-metabolic conditions, dementia at the later stages, Hashimoto encephalopathy).[4]

CSF protein assays based on protein 14-3-3 or total tau detection have higher sensitivity and specificity than EEG recording, the latter ranging from 80% to 95% in most studies, but remain of moderate diagnostic accuracy, especially in cases that are associated with a low pretest probability of having sCJD.[5]

A relatively high sensitivity and specificity for sCJD have also been reported for brain MRI[6]; around 80% of patients have been reported to have DWI or FLAIR abnormalities in cortex or deep gray matter structures (striatum and thalamus).[6,7]

Recently, Vitali et al.[8] suggested that prevalence of DWI over FLAIR abnormalities, implying restricted diffusion, is one of the most important criteria for diagnosing sCJD, suggesting also that the presence of hypointense regions on ADC is a supportive feature of sCJD and may be helpful to distinguish mimicking diseases. Moreover, only sCJD cases had DWI subcortical hyperintensity correlating with ADC hypointensity in the same regions: this finding is highly specific for sCJD in the proper clinical context.[8]

Given the phenotypic heterogeneity of sCJD, a correlation between MRI lesion patterns and molecular subtypes has also been attempted.[9] Although the cerebral cortex, basal ganglia, and thalamus showed a different pattern of involvement among sCJD subtypes, hippocampal signal alterations in both DWI and FLAIR were present in more than 30% of patients,[8] including the MV1 subtype.[9]

In our case of rapidly progressive dementia, the brain MRI abnormalities, EEG findings, and elevation of CSF 14-3-3 and tau protein were initially compatible with a clinical diagnosis of probable sCJD. Only the clinical course and the positivity for anti-LGI1 antibodies led to the right diagnosis. The presence of faciobrachial tonic seizures that may be associated with VGKC antibody–associated encephalitis led us to the decision to treat with immunosuppressants even though the hypothesis of autoimmune encephalitis was not supported by the initial imaging and laboratory findings. Indeed, VGKC antibody–associated encephalitis is a significant diagnostic challenge to clinicians due to its rarity and substantial heterogeneity. Rapidly progressive cognitive decline, behavioral changes, depression, emotional lability, and seizures are the most frequent clinical presentation of the disease.[4] Treatment for VGKC antibody–associated encephalitis involves immunosuppressive therapy consisting of plasma exchange or IV immunoglobulin followed by oral corticosteroids. A prior case series has shown that combination of these agents resulted in a decrease in the levels of serum VGKC antibodies and in a variable improvement of neuropsychological functioning,[10] as in our case.

Clinical, radiologic, electrophysiologic, and laboratory findings in VGKC antibody–associated encephalitis may overlap with those of sCJD, leading to a difficult differential diagnosis. All individuals with rapidly progressive dementia should be assessed for the possibility of antibody-mediated encephalitis. This assessment should include early serum testing for antibodies against voltage-gated potassium channels. While awaiting final serologic results in patients with a rapidly progressive dementing illness, it may be reasonable to try an empiric course of immunomodulatory therapy.

AUTHOR CONTRIBUTIONS

Dr. Cavallieri: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript. Dr. Mandrioli: study concept and design, acquisition of data, analysis and interpretation of data, drafting of the manuscript, study supervision. Dr. Tondelli: study concept and design, analysis and interpretation of data, drafting of the manuscript, study supervision. Dr. Vitetta: study concept and design, acquisition of data, analysis and interpretation of data, study supervision. Dr. Stipa: study concept and design, analysis and interpretation of data. Dr. Vallone: acquisition of data, analysis and interpretation of data, study supervision. Dr. Georgoulopoulou: acquisition of data, analysis and interpretation of data. Dr. Barbi: acquisition of data, analysis and interpretation of data. Prof. Liguori: acquisition of data, analysis and interpretation of data. Dr. Parchi: acquisition of data, analysis and interpretation of data, drafting of the manuscript, study supervision. Prof. Nichelli: study concept and design, study supervision.

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DISCLOSURE

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REFERENCES

1. Castellani RJ, Colucci M, Xie Z, et al. Sensitivity of 14-3-3 protein test varies in subtypes of sporadic Creutzfeldt-Jakob disease. Neurology 2004;63:436–442.
2. Geschwind MD, Tan KM, Lennon VA, et al. Voltage-gated potassium channel autoimmunity mimicking Creutzfeldt-Jakob disease. Arch Neurol 2008;65:1341–1346.
3. Parchi P, Giese A, Capellari S, et al. Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. Ann Neurol 1999; 46:224–233.
4. Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL. Rapidly progressive dementia. Ann Neurol 2008;64: 97–108.
5. Parchi P, Capellari S. Prion disease: diagnostic value of cerebrospinal fluid markers. Nat Rev Neurol 2013; 9:10–11.
6. Zerr I, Kallenberg K, Summers DM, et al. Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. Brain 2009;132:2659–2668.
7. Mihara M, Sugase S, Konaka K, et al. The "pulvinar sign" in a case of paraneoplastic limbic encephalitis associated with non-Hodgkin's lymphoma. J Neurol Neurosurg Psychiatry 2005;76:882–884.
8. Vitali P, Maccagnano E, Caverzasi E, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. Neurology 2011;76:1711–1719.
9. Meissner B, Kallenberg K, Sanchez-Juan P, et al. MRI lesion profiles in sporadic Creutzfeldt-Jakob disease. Neurology 2009;72:1994–2001.
10. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. Brain 2004;127:701–712.

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