Autoimmune encephalitis mimicking Creutzfeldt-Jakob disease

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We present a patient with rapidly progressive dementia (RPD) clinically suspicious for prion disease who met clinical criteria for probable and proposed MRI criteria for definite sporadic Creutzfeldt-Jakob disease (sCJD) but was found to have autoimmune encephalitis (AE).^{1,2}

Case report

A 69-year-old man with a history of smoking and tremor presented with RPD. During the prior 3 weeks, he lost his job and became increasingly confused, with worsening tremor and difficulty ambulating. At admission, he was oriented to self and setting, had poor recent and remote memory, and could not follow complex commands. There was moderate expressive aphasia with frequent paraphasic errors. Diffuse parietal, a right parietal drift, tremor of the hands, poor coordination of rapid alternating movements, and brisk right deep tendon stretch reflexes were noted. He listed to the right when walking.

Testing revealed hyponatremia (133 mEq/L) and CSF studies showed 1 leukocyte, protein 68 mg/dL, and glucose 91 mg/dL, without evidence of infection. CSF 14-3-3 and tau protein assay results were pending during hospitalization.

Admission diffusion-weighted image (DWI) brain MRI demonstrated hyperintense cortical ribboning throughout the left hemisphere with corresponding hypointensity on apparent diffusion coefficient (ADC) mapping, sparing bilateral caudate nuclei and putamen (figure, A and B). Admission EEG was low voltage with slight left hemispheric slowing in the delta/theta range, without periodic sharp-wave complexes commonly associated with prion disease.

On day 6 the patient followed no commands, and had right facial myoclonus, right hemineglect, and severe ataxia.

Antithyroperoxidase antibody level was 528 WHO units/mL blood. CT demonstrated a thyroid nodule and a 4-mm right upper lung nodule with 1 prominent hilar lymph node. Whole-body FDG-PET on day 8 demonstrated increased uptake in the left posterior cingulate

Practical Implications

In patients presenting with rapidly progressive dementia, brain FDG-PET imaging may be helpful in distinguishing patients with autoimmune encephalitis from those with Creutzfeldt-Jakob disease.

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Figure MRI and fluorodeoxyglucose-PET imaging

(A) Diffusion-weighted image shows hyperintense cortical ribboning throughout the left hemisphere with (B) corresponding restricted diffusion on apparent diffusion coefficient map, better seen in the left precuneus (large arrow) and cortical gray matter (small arrows) sparing the bilateral caudate nuclei and putamen. (C) On fluid-attenuated inversion recovery, no conspicuous hyperintense signal is noted in the left cerebral cortex. (D-F) In a separate study, FDG-PET showed increased uptake in the left posterior cingulate gyrus, left posterior frontal cortex, left occipital cortex, left thalamus, and left precuneus.

gyrus, posterior frontal cortex, occipital cortex, thalamus, and precuneus (figure, D-F). EEG 9 days after admission again showed low voltage without an alpha rhythm.

On day 9, treatment with high-dose IV steroids and IV immunoglobulins was initiated for a 5-day course. By day 13, the patient was fully orientated with improved memory, was able to follow commands, had fluent speech, and walked unassisted. The myoclonus and hemineglect resolved. Three days after hospital discharge, the autoantibody assays showed raised neuronal voltage-gated potassium channel (VGKC) antibody and P/Q-type calcium channel antibody titers (0.05 nmol/L and 0.07 nmol/L, respectively; normal ≤ 0.02 nmol/L). CSF 14-3-3 protein was detected and tau protein was 1,152 pg/mL (normal $\leq 1,150$ pg/mL). Thyroid nodule and hilar lymph node biopsies were unremarkable.

DISCUSSION

This patient with RPD met clinical criteria for probable and proposed MRI criteria for definite sCJD, contrary to prior reports of AE mimicking sCJD.¹⁻³ Autoimmune conditions are common and potentially treatable nonprion RPD etiologies.⁴ His smoking history, hyponatremia, pulmonary and thyroid nodules, and prominent hilar lymph node raised concern for an AE. In addition, CSF protein is not typically elevated in sCJD.^{1,4} A similar presentation has been reported in 2 cases with VGKC autoimmunity.⁵

Both asymmetric DWI/fluid-attenuated inversion recovery (FLAIR) hyperintensities and hypointense ADC maps in the cingulate, striatum, or cortex have been cited in differentiating sCJD from nonprion RPD, with DWI hyperintensities reportedly more sensitive than FLAIR abnormalities in sCJD.^{1,2,4} Conversely, cortical DWI hyperintensity with normal ADC mapping has been described in VGKC autoimmunity, a point of distinction of AE from sCJD.^{4,5} The AE case presented here contradicts these descriptions. Of note, qualitative and quantitative evaluation of ADC maps for changes in cortical gray matter signal is challenging due to

close proximity to hyperintense subarachnoid CSF signal, especially in the absence of associated abnormal subcortical signal.²

Brain FDG-PET was obtained to distinguish sCJD from AE, with cerebral hypermetabolism suggesting an autoimmune process.^{6,7} In the absence of evidence of an infectious or primary malignant process, the brain FDG-PET findings prompted the initiation of first-line immunomodulatory therapy, suggesting further utility of this modality beyond occult malignancy screening in the evaluation of RPD.⁴ Confirmatory serum autoantibody results arrived after discharge.

Diagnostic, clinical, and economic challenges are encountered when evaluating a patient with RPD, including the complexity and cost of investigation and delayed diagnosis. Often, effective therapies are delayed, or a false diagnosis pursued and presumptively treated. A graver concern is a premature transition to primarily palliative care in the face of an “untreatable” illness such as sCJD. Early treatment of suspected AE may decrease morbidity and mortality, yet autoantibody detection can be misleading and must be interpreted within the appropriate clinical context. Clinical comparisons between these disorders are warranted, with refinement of diagnostic and treatment paradigms for purposes of clinical efficiency, cost-effectiveness, and improvement in outcome.

REFERENCES

1. World Health Organization. Global surveillance, diagnosis, and therapy of human transmissible spongiform encephalopathies: report of WHO consultation. In: *Emerging and Other Communicable Diseases, Surveillance and Control*. Geneva: World Health Organization; 1998:1–26.
2. Vitali P, Maccagnano E, Caverzasi E, et al. Diffusion-weighted MRI hyperintensity patterns differentiate CJD from other rapid dementias. *Neurology* 2011;76:1711–1719.
3. Grau-Rivera O, Sanchez-Valle R, Saiz A, et al. Determination of neuronal antibodies in suspected and define Creutzfeldt-Jakob disease. *JAMA Neurol* 2014;71:74–78.
4. Geschwind MD, Shu H, Haman A, Sejvar JJ, Miller BL. Rapidly progressive dementia. *Ann Neurol* 2008;64:97–108.
5. Geschwind MD, Tan KM, Lennon VA, et al. Voltage-gated potassium channel autoimmunity mimicking Creutzfeldt-Jakob disease. *Arch Neurol* 2008;65:1341–1346.
6. Kim EJ, Cho SS, Jeong BH, et al. Glucose metabolism in sporadic Creutzfeldt-Jakob disease: a statistical parametric mapping analysis of (18) F-FDG PET. *Eur J Neurol* 2012;19:488–493.
7. Baumgartner A, Rauer S, Mader I, Meyer PT. Cerebral FDG-PET and MRI findings in autoimmune limbic encephalitis: correlation with autoantibody types. *J Neurol* 2013;260:2744–2753.

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