Cortical and bithalamic hypometabolism by FDG-PET/CT in a patient with sporadic fatal insomnia

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A 29-year-old woman presented with 1 year of cognitive and functional decline. She had resided in the Netherlands in the 1990s, and had no relevant family history. Twelve months prior to presentation, her family noted that she seemed apathetic. She developed daytime fatigue and was in an automobile accident attributed to sleepiness. Over 1 month, she developed difficulty with job-related tasks, episodic slurred speech, intermittent diplopia, insomnia, delusions, hallucinations, and difficulty in navigating familiar driving routes.

Following a second automobile accident 4 months later, an emergency department evaluation found B₁₂ deficiency (207 pg/mL, normal 211–911 pg/mL) and the patient was given supplementation. Brain MRI demonstrated nonspecific T2/fluid-attenuated inversion recovery white matter hyperintensities (figure, A–F). Polysomnography demonstrated sleep duration of less than 4 hours, prolonged sleep onset and REM latency, and apnea hypopnea index of 24.7, leading to diagnosis of moderate obstructive sleep apnea.

At 9 months after onset of symptoms, the patient was unable to walk independently. She was treated empirically with IV methylprednisolone (1 g daily for 2 days) followed by oral taper, which was discontinued due to hallucinations. She then received an empiric course of IV immunoglobulin (2 g/kg), without benefit. Twelve months after symptom onset, she was dependent in all activities of daily living, prompting admission to a tertiary facility.

At admission, the patient was at times tearful, with an otherwise flat affect. She scored 7 of 30 on the Montreal Cognitive Assessment, with deficits in orientation, visuospatial and executive abilities, memory, and calculation. Neurologic examination demonstrated hemineglect, ideomotor apraxia, nonfluent speech, scanning dysarthria, restricted upgaze, frontal release signs, parosmia, and polyminimyoclonus. She was unable to stand or ambulate independently.

Hematologic, metabolic, infectious, inflammatory, and neoplastic evaluations were unremarkable, including CSF studies. Brain MRI (figure, G–L) was concerning for cortical and subcortical diffusion restriction. EEG demonstrated rhythmic delta activity and focal slowing. FDG-PET/CT demonstrated diffuse cortical and bithalamic hypometabolism (figure, M). In light of these findings and history, the patient was diagnosed with probable sporadic Creutzfeldt-Jakob disease (sCJD), with concern for possible variant Creutzfeldt-Jakob disease (vCJD).¹

Six days after discharge to hospice, the remaining studies resulted normal or negative: paraneoplastic autoantibody panels (CSF and serum), CSF 14-3-3, tau level, and real-time quaking-induced conversion (RT-QuIC) test. Nine days after discharge, the patient died. Brain-only autopsy demonstrated spongiform changes and gliosis of the olivary nucleus and thalamus (figure, N and O). Monoclonal antibody immunohistochemical staining for the prion protein

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(A–F) Brain MRI within 1 month of symptoms onset, initially interpreted as normal but on retrospective review of diffusion-weighted imaging demonstrating patchy areas of increased signal in a cortical ribbon pattern designated by blue arrows (e.g., high right parasagittal parietal, bilateral frontal parasagittal, bilateral posterior temporoparietal, and insular regions). These areas are not conspicuous on fluid-attenuated inversion recovery sequences; correlation with apparent diffusion coefficient map was present. (G–L) Brain MRI at 12 months of symptoms with less conspicuous diffusion restriction within the cortical gyri over the cerebral convexities, though evident in the right caudate. (M) At 12 months of symptoms, a brain [^{18}F] FDG-PET/CT 3D-SSP hypometabolism map was generated using the CortexID database and GE advanced workstation package (GE Healthcare, Waukesha, WI), with higher Z scores indicating lower metabolism. Diffuse hypometabolism, particularly of the right greater than left parietal cortex as well as the bilateral thalami (white arrows), was demonstrated. (N, O) Hematoxylin & eosin staining of the (N) inferior olivary nucleus and (O) dorsomedial nucleus of the thalamus demonstrate neuronal loss, reactive astrocytosis, and gliosis ($\times 200$ magnification). (P) Immunohistochemical staining with the 3F4 antibody demonstrates granular immunoreactivity involving the entorhinal cortex ($\times 200$ magnification). These histopathologic and immunologic features combined with the presence of type 2 prion protein by Western blot confirm the diagnosis of sporadic fatal insomnia.

(3F4) demonstrated granular deposits (figure, P). Western blot and *PRNP* sequencing confirmed a diagnosis of sCJD MM2 thalamic or sporadic fatal insomnia (sFI) (NPDPSC).²

Discussion

With only 12 individual autopsy and disease-related prion protein cases reported in the United States, sFI is rare and diagnosis is difficult.³ It can be clinically indistinguishable from fatal familial insomnia (FFI) and difficult to differentiate from sCJD and vCJD. Distinguishing features include lack of family history or *PRNP* gene mutation, normal 14-3-3 and tau, negative CSF RT-QuIC, and subtle or nonspecific MRI findings.^{4,5} RT-QuIC testing from the olfactory mucosa has been shown to be positive in FFI, though this has yet to be shown in sFI.⁶ Similar to vCJD, *PRNP* is methionine homozygous at codon 129. Fatal insomnia presents at a younger age (mean 46 years, range 13–74) with longer duration of illness (mean 24 months, range 10–73 months), characterized by ataxia, visual signs, dementia, tremor, myoclonus, and spasticity, as well as insomnia, psychiatric symptoms, and autonomic dysfunction.^{3,4} Classic CJD symptoms often occur late.^{3,4}

This case epitomizes the difficulty in diagnosing this rare disease given the heterogeneity of its clinical presentation and the lack of findings seen in the comparatively more common sCJD. In retrospect, sleep disturbance was a prominent early aspect of the patient's clinical presentation. The importance, however, was not initially appreciated due to confounding concerns including possible head trauma, diagnosis of obstructive sleep apnea, young age, lack of similar family history, the relative rarity of sFI, and history of residing in Europe at a time of heightened concern for vCJD. In this case, the results of diagnostic studies utilized for diagnosis of sCJD were subtle or normal, consistent with prior observations in sFI.^{4,5} The most helpful clinical features were sleep disturbance, dementia, and late classic CJD signs, with lack of vCJD or sCJD imaging and laboratory findings and cortical and bithalamic hypometabolism on FDG-PET/CT.^{3,7} While this patient received sedation in order to undergo FDG-PET/CT, the hypometabolism was marked. Thus, brain FDG-PET/CT may play a role in the evaluation of rapidly progressive dementia, particularly when EEG, CSF, and MRI testing are normal or findings are subtle.

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The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC.

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References

1. WHO. Global Surveillance, Diagnosis and Therapy of Human Transmissible Spongiform Encephalopathies: Report of a WHO Consultation. Geneva: WHO; 1998.
2. Parchi P, Capellari S, Chin S, et al. A subtype of sporadic prion disease mimicking fatal familial insomnia. *Neurology* 1999;52:1757–1763.
3. Cracco L, Appleby BS, Gambetti P. Fatal familial insomnia and sporadic fatal insomnia. *Handb Clin Neurol* 2018;153:271–299.
4. Gambetti P, Kong Q, Zou W, Parchi P, Chen SG. Sporadic and familial CJD: classification and characterisation. *Br Med Bull* 2003;66:213–239.
5. Montagna P, Gambetti P, Cortelli P, Lugaresi E. Familial and sporadic fatal insomnia. *Lancet Neurol* 2003;2:167–176.
6. Redaelli V, Bistaffa E, Zanusso G, et al. Detection of prion seeding activity in the olfactory mucosa of patients with Fatal Familial Insomnia. *Scientific Rep* 2017;7:46269.
7. Perani D, Cortelli P, Lucignani G, et al. [18F]FDG PET in fatal familial insomnia: the functional effects of thalamic lesions. *Neurology* 1993;43:2565–2569.