Positron emission tomography imaging in a case of E200K mutation-related spongiform encephalopathy with non-diagnostic magnetic resonance imaging and cerebrospinal fluid testing

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Abstract
Objective: Creutzfeldt–Jakob disease is a rapidly progressive spongiform encephalopathy. The E200K mutation is found in a majority of genetically transmitted Creutzfeldt–Jakob disease cases. Methods: We describe the case and associated neuroimaging of an E200K-129M gene-mutation-related fatal spongiform encephalopathy with resultant clinical insomnia and thalamic changes. Results: A 46-year-old Caucasian male presented with, who was well until 2 months prior to admission, a rapidly progressive dementia followed by a change in personality with auditory and visual hallucinations. His wife noted progressively worsening jerking and other limb movements and that he kept his eyes open overnight and was “awake” at all hours. Magnetic resonance imaging, electroencephalogram and initial cerebrospinal fluid analysis were essentially non-diagnostic. Positron emission topography revealed severe bilateral thalamic hypometabolism. Posthumous cerebrospinal fluid analysis revealed abnormal PrP 27-30 protein. Autopsy confirmed prion disease and presence of the E200K-129M mutation. Conclusion: This report highlights that positron emission topography imaging may help diagnose E200K-129M mutation-related spongiform encephalopathy. In cases of non-diagnostic magnetic resonance imaging, electroencephalogram and cerebrospinal fluid studies, early positron emission topography may help in the workup of rapidly progressive dementia.

Keywords
Prion disease, Creutzfeldt–Jakob disease, E200K

Introduction
Creutzfeldt–Jakob disease (CJD) is a rare, rapidly progressive and eventually fatal spongiform encephalopathy. Mutations in prion protein genes (PrP) are associated with spongiform encephalopathy and disruption in their function are acquired, sporadic or genetic in origin.¹ The E200K mutation is found in a majority of genetically transmitted CJD cases and was first identified in patients of Eastern European origin and among Libyans of Jewish ancestry.² E200K mutations and other genetic prion diseases have been classified into three major groupings based on clinical and pathological features: familial CJD, Gerstmann–Sträussler–Scheinker (GSS) disease and familial fatal insomnia (FFI).³,⁴ Carriers of the E200K mutation generally develop familial CJD and are often asymptomatic for decades, however, survive only a few months to years after becoming symptomatic.³–⁵ Selective changes of the thalamus in these patients

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can appear on single photon emission computed tomography (SPECT) imaging, and these changes can be present for years prior to symptom onset.6,7 Studies on E200K mutation familial CJD patients and those with FFI also demonstrate that magnetic resonance imaging (MRI) can show non-specific and limited changes resembling those seen in sporadic CJD.8,9 Additionally, electroencephalogram (EEG) abnormalities in patients with E200K mutations, most notably periodic synchronous discharges (PSDs), have been shown to appear similar to patients with sporadic CJD.10 Single case reports are exempt from the local Institutional Board Review approval.

Case report

We report the case of a 46-year-old Caucasian male who was well until 2 months prior to admission. Although he was of Eastern European (non-Jewish) ancestry, there was no known family history of dementia and his parents were still living and healthy. The patient suffered a rapidly progressive dementia followed by a change in personality with auditory and visual hallucinations. His wife noted progressively worsening jerking and other limb movements and that he kept his eyes open overnight and appeared awake. He was referred by psychiatry to our institution for further evaluation.

Over his 1-week hospitalization, the patient demonstrated a continued clinical deterioration in mental status. He developed a profound dementia with an inability to form complete sentences and displayed bilateral jerking movements, frontal release signs and diffuse hyper-reflexia. Symptoms progressed to akinetic mutism. MRI done under anesthesia was essentially unremarkable for an acute process (Figure 1). Positron emission topography (PET) imaging, however, revealed severe bilateral thalamic hypometabolism (Figure 2). Continuous video EEG was analyzed over a period of 48 h and reported showing only intermittent generalized slowing with no noticeable sleep architecture identified throughout the study. No epileptiform discharges were identified. No irregular breathing patterns or dysautonomic events suggestive of FFI were noticed during his hospital stay.

Cerebrospinal fluid (CSF) analysis revealed an ambiguous 14-3-3 result and a negative tau amount of 72 pg/mL (decision point 1150 pg/mL) both non-indicative of spongiform encephalopathy. An abnormal protease-resistant prion protein, PrP 27-30, was only posthumously identified in the CSF. A clinical sleep study was ordered; however, the patient continued to clinically deteriorate and the study was not possible. He was discharged to hospice and passed away. From the time of symptoms onset to death was about 3 months. Brain autopsy revealed histopathological and immunohistochemical evidence of prion protein deposits and presence of the E200K-129M gene-mutation consistent with the diagnosis of familial CJD. No other neuropathological results were made known to us following his death.

Discussion

The patient in this report had a rapidly progressive dementia, bilateral myoclonus, a startle response and diffuse pathological hyper-reflexia that developed over a 2-month period. These findings are often hallmarks seen in both sporadic and genetic variants of CJD. His MRI diffusion, T2-fluid-attenuated inversion recovery (FLAIR) and EEG, however, did not have findings sometimes described in patients with CJD. For example, he did not have insular or cortical hyper-intensities on MRI-DWI nor did he have PSDs on EEG. By history, he was suffering from severe insomnia and radiologically his PET scan showed marked thalamic hypometabolism. These findings are suggestive of E200K-related familial prionopathy. Although he had sleep disturbances...
and primarily thalamic involvement, a diagnosis of FFI could not be assumed due to lack of histochemical test results, a clinical sleep study and the time course of disease. Additionally, the D178N mutation, commonly associated with FFI, was also not identified in his autopsy pathology report. A number of familial CJD patients have a similar progression of disease with significant sleep disturbances and the E200K mutation diagnosis is generally associated with a median life expectancy of about 18 months from the time of diagnosis. Nevertheless, PET imaging can potentially help diagnose E200K mutation-related spongiform encephalopathy, particularly in cases where brain MRI, CSF findings and EEG are non-revealing.

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