A 65-year-old man initially experienced difficulty forming his tie and felt unsteady while driving. Days later, these symptoms were followed by periods of dizziness and vague episodes of confusion that he felt were “out of character.” The patient was extremely concerned, especially given a strong family history of strokes. With an unremarkable physical examination, laboratory tests, and brain imaging, the patient’s symptoms were attributed to his inadvertent ingestion of codeine-containing medication and to multiple increasing life stressors, including recent prostatectomy for prostate cancer.

One week later, the patient returned complaining of significant confusion, problems opening doors, and progressive difficulty performing activities of daily living. Physical examination at this time revealed the patient to be confused with notable psychomotor retardation. Decreased left arm swing was noted on gait exam. An electroencephalogram (EEG) showed findings of right temporal slowing. Because of this finding and the patient’s deteriorating mental status, he was admitted for further evaluation.

Repeat EEG demonstrated bihemispheric triphasic wave complexes. Cerebrospinal fluid cytology and cultures were normal, but cerebrospinal fluid protein 14-3-3 was abnormally elevated. Magnetic resonance imaging (MRI) of the brain revealed areas of diffusion restriction in the right cerebral cortex and right basal ganglia (Figure 1). No abnormalities were found after extensive laboratory tests, including a metabolic panel and tests for syphilis, HIV, herpes simplex virus, human herpesvirus-6, C-reactive protein, antinuclear antibodies, folate, erythrocyte sedimentation rate, and homocysteine levels.

His neurologic condition continued to deteriorate rapidly. Without effective treatment options, he was referred to hospice and succumbed to his disease process approximately 2 months from the time of initial presentation.

A limited autopsy of the brain was performed at the National Prion Disease Pathology Surveillance Center at Case Western Reserve University in Cleveland, Ohio. An abnormal prion protein was detected and characterized by Western blot, histopathological studies, and immunohistochemical examinations.

Figure 1. (a, b, c) Multiple axial images from the patient’s brain MRI demonstrate abnormal signal hyperintensity (arrows) at several cortical locations and in the caudate head on the diffusion-weighted sequence. (d, e, f) Less conspicuous signal hyperintensity is present at the corresponding locations on the fluid-attenuated inversion recovery (FLAIR) sequence.

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DIAGNOSIS: Sporadic Creutzfeldt-Jakob disease (sCJD). Genetic sequencing of the proteinase-resistant protein (PrP) ruled out the presence of a pathologic genetic mutation in the coding region of the PrP gene. Therefore, the prion disease in this case was not familial.

DISCUSSION

Creutzfeldt-Jakob disease (CJD) is a rare but invariably fatal neurodegenerative illness caused by accumulation of an abnormal form of a PrP, or prion, in the brain parenchyma. Detection of the pathologic prion (PrPSc) in brain tissue that also demonstrates neuropathologic changes of spongiform degeneration, neuronal death, and astrocitic gliosis allows for the definitive diagnosis of CJD (1–3) (Figure 2). Multiple forms of CJD have been described, with sporadic being the most commonly documented form (85% of cases). Although routes or sources of infection are not known, six molecularly distinct phenotypes of sCJD have been defined (2). Each subtype differs with regard to various clinicopathologic features (including age of onset, disease duration, EEG and 14-3-3 findings) and pattern of histopathologic changes (2, 4, 5).

Other forms of CJD are variant, familial, and iatrogenic CJD. Variant CJD has been reported mainly in Europe, where ingestion of products from cattle infected with bovine spongiform encephalopathy is the suspected route of transmission and has received much worldwide press coverage in recent years. Familial CJD is exceedingly rare and is inherited as a germline mutation in the human prion protein gene (PRNP) (6). Iatrogenic causes include ingestion of contaminated human hormone supplements, corneal transplantation, and transplantation of cadaveric dura mater, which was previously common in Japan before becoming the focus of heavy public scrutiny (7–10).

CJD, especially in its early stages, is an extremely challenging disease to diagnose. The clinical symptoms are relatively nonspecific and overlap with other dementia disorders. The characteristic EEG findings are seen in only 66% of patients and have a reported specificity of 74% (11, 12). Detection of 14-3-3 protein in cerebrospinal fluid can support the diagnosis and is positive in over 90% of patients with CJD. The presence of this protein should not be considered pathognomonic, however, as it can also be detected in the setting of encephalitis, stroke, hypoxic brain injury, intracranial bleed, and Alzheimer's disease (13, 14). Computed tomography scans of the brain may show either nonspecific atrophy or no abnormality at all. Brain biopsy can be conclusive, but the elevated risk of disease transmission makes this a rarely plausible option. Given this diagnostic dilemma, MRI of the brain is an increasingly useful tool in the evaluation of patients with suspected CJD. Most importantly, MRI is helpful in excluding other possibly treatable causes of encephalopathy.

Clinical presentations of CJD are variable, depending on the stage of disease. A majority of patients demonstrate rapidly progressing mental decline, with onset of dementia, ataxia, and sometimes visual disturbances within a few weeks to several months. Development of myoclonus often occurs with disease progression, coinciding with periodic sharp wave complexes that are detectable on EEG (7, 15). The late phase begins after several months and is dominated by akinetic mutism, with death typically occurring within a year.

Early in the disease course, brain MRI may be without abnormality. In fact, absence of significant findings on all MRI sequences throughout the course of sporadic CJD has been reported in some cases (16, 17). However, the large majority of patients with CJD demonstrate the characteristic imaging features of the disease, specifically when fluid-attenuated inversion recovery (FLAIR) and diffusion-weighted imaging (DWI) sequences are employed as part of the imaging protocol. It has been repeatedly shown that DWI is more sensitive in the detection of parenchymal abnormalities than FLAIR (18–20). Another benefit of DWI, especially in patients with myoclonus, is the short acquisition time (approximately 30–45 seconds). DWI also offers the advantage of detecting the typical imaging features of stroke and confirming the presence or absence of this key alternative differential diagnosis.

Isolated cortical hyperintensity and combined cortical and deep gray matter (basal ganglia) hyperintensity are the two patterns of DWI and/or FLAIR abnormality that have been described (21). One study has shown that 95% of patients demonstrate signal abnormality in at least three out of four discrete areas, to include the insula, cingulate gyrus, superior frontal gyrus, and occipital gyrus (22). Though not a specific finding, one should recognize these isolated cortical hyperintensities as a pattern of suspicion for CJD in the setting of cognitive decline or other characteristic clinical findings (21). Resolution of findings, pathologic enhancement, and cerebral edema are not commonly described imaging characteristics of CJD and can be useful findings when considering the differential diagnosis for CJD.

It is thought that involvement of the basal ganglia is a relatively late development in the course of the disease, and up to 33% of patients with CJD can present without basal ganglia hyperintensity (21, 23). There is potential clinical significance associated with involvement of the deep gray matter, as a short disease course with rapidly progressing neurologic deterioration has been linked with the presence of basal ganglia imaging abnormality. In contrast, absence of basal ganglia involvement correlates with delayed onset of dementia and an extended disease course (24, 25).

DWI is more sensitive than FLAIR in the detection of cortical abnormalities, especially in early stages of CJD. Several studies have shown that areas of the brain cortex with abnormal MRI signal have more severe histologic findings than areas with normal cortical signal.
In conclusion, CJD is more often a diagnosis of exclusion, requiring also a constellation of clinicopathologic attributes and supportive diagnostic examination. Undoubtedly, MRI utilizing FLAIR and DWI should be an essential component in the evaluation of patients with progressive cognitive decline. The ability to detect the presence of FLAIR signal abnormalities is relatively more frequent than the prevalence of FLAIR signal elevation is thought to coincide with the stages of CJD during which gross is the more widespread neuropathologic finding (28).

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