CASE REPORT

Creutzfeldt–Jakob disease with unusual presentation of peripheral neuropathy and ophthalmoplegia

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ABSTRACT

Creutzfeldt–Jakob disease (CJD) is a well-described disease. It is characterized by rapidly progressive dementia, myoclonus, ataxia, pyramidal, and extrapyramidal signs. There are well-defined electroencephalogram and magnetic resonance imaging (MRI) findings, and markers found in the cerebrospinal fluid (CSF). The gold standard for diagnosing CJD remains brain biopsy. We present a case of a patient with a family history of biopsy-proven CJD who initially presented with symptoms of peripheral neuropathy. A month later, he developed ataxia, ophthalmoparesis, and then dysarthria. His initial workup was relatively unrevealing, showing an elevated protein in his CSF. He was thought to have Miller Fisher syndrome variant of Guillain–Barré syndrome. He neither, however, responded to plasmapheresis nor IVIG. He later started to develop progressive dementia. Repeated MRI showed restricted diffusion in the caudate and putamen, as well as in the cortex (cortical ribboning). Lumbar puncture was then found to be positive for 14-3-3 protein, total-tau protein, and real-time quaking-induced conversion assay, which are highly suggestive of CJD. We present a case of CJD with an unusual presentation resulting in misdiagnosis, prolonged workup, and potentially harmful treatment modalities. This case highlights the importance of broadening our definition of CJD to encompass more cases with unusual presentations.

Key words: Ataxia, Creutzfeldt–Jakob disease, dementia, neuropathy, ophthalmoplegia

INTRODUCTION

Creutzfeldt–Jakob disease (CJD) is a human prion disease, a rare disorder, which has been well described with a characteristic clinical presentation. This involves rapidly progressive dementia, myoclonus, ataxia, pyramidal, and extrapyramidal signs. Electroencephalogram (EEG) often has periodic sharp wave complexes. Magnetic resonance imaging (MRI) has been described as having diffuse-weighted imaging (DWI) and T2 hyperintensities in the basal ganglia along with cortical ribboning pattern. Lumbar puncture can be helpful in identifying protein markers associated with CJD. Despite increased understanding of the clinical signs and symptoms of CJD, the gold standard for diagnosis remains brain biopsy.[1]

As our understanding of the disease grows, so does the recognition of variations to the accepted prototypical description of CJD. With the identification of sporadic, variant, familial, and iatrogenic CJD, we have several other well-described syndromes in the CJD spectrum. Familial CJD is seen in approximately 10%–15% of cases with CJD. Mutations are often seen in the PrP gene on Codon 129 and are often inherited in an autosomal dominant pattern. Patients with familial CJD often present without the typical EEG findings seen in CJD and 50% of them do not have

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14-3-3 proteins in their cerebrospinal fluid (CSF),[2] which often makes the diagnosis more challenging. Some patients with familial CJD have been described as having a much earlier onset of symptoms and a more prolonged course of 5–11 years as opposed to 6 months–1-year life expectancy from the time of diagnosis usually seen in sporadic CJD.[2,3]

Other phenotypes and varied presentations have been reported in the literature for CJD. Patients have been rarely reported to present with a bulbar symptom.[4] Psychiatric onset with Parkinsonian features and ophthalmoparesis, which appeared consistent with progressive supranuclear palsy, has been described in the literature.[5,6] There have also been anecdotes of CJD presenting as a painful peripheral neuropathy.[7,8] We present a unique case of CJD, which initially presented with peripheral neuropathy followed thereafter by ophthalmoparesis which early in the course of the illness was misdiagnosed as Miller Fisher syndrome (MFS) variant of Guillain–Barré syndrome (GBS).[9,10]

CASE REPORT

A 60-year-old Caucasian male with medical history of psoriatic arthritis on adalimumab and methotrexate presented to his primary care physician with burning sensation in his feet and unintentional 14-pound weight loss over a period of 3 months. He did not have a history of diabetes mellitus or alcohol abuse. He had worked for a bank. His examination was notable for sensory impairment in the stocking distribution and diminished reflexes suggestive of peripheral neuropathy. He was referred to neurology for further evaluation of his neuropathy. As a workup for peripheral neuropathy, B12, thiamine level, serum protein electrophoresis, and thyroid function tests were checked and found to be negative. Nerve conduction studies and electromyography revealed sensorimotor polyneuropathy with axonal and demyelinating features.

One month later, he presented to the Emergency Department with episodic diplopia and ataxia. Episodes were characterized as brief (seconds to minutes) and happened multiple times a day, without any provoking factors. He denied any chewing or swallowing problems. He did endorse difficulty getting up from a chair as well as gait unsteadiness. He was alert and oriented with good fund of knowledge. Physical examination was significant for hypophonia, mild hoarseness, and dysarthria. His extraocular movements showed difficulty with vertical eye movements, worse with upward gaze with intact horizontal gaze. He was found to have dysmetria, which was noted in all extremities. His gait was wide-based and ataxic.

Given the patient's presentation of progressive neuropathy, ataxia and ophthalmoplegia, MFS variant of GBS was considered high in the list of differential diagnosis. Other differential diagnoses were CSF infection, given his relative immunosuppression with adalimumab and methotrexate, primary CNS neoplastic, and a paraneoplastic process. CJD was also considered, especially given the patient's family history. However, since the patient had no cognitive impairment, the possibility of CJD was deemed to be less likely.

MRI brain with and without contrast [Figure 1a] was performed and read as unremarkable with no abnormalities on DWI. CSF analysis showed WBC of 0, RBC of 0, protein of 72 mg/dl (normal 15–45 mg/dl), and glucose of 65 mg/dl (normal 40–70 mg/dl). Serum and urine protein electrophoresis were normal.

The patient was started on plasmapheresis. In the interim, results of paraneoplastic antibodies, namely Anti-Hu, anti-neuronal nuclear autoantibody type 2 (ANNA-2), ANNA-3, amphiphysin antibody, Purkinje cell cytoplasmic antibody type-1 (PCA-1), PCA-2, collapsin response mediator protein-5, and anti-N-methyl-D-aspartate returned and were negative. Acetylcholine receptor antibodies, Lyme's titer, and Anti-GQ1b ganglioside antibodies were also negative.

During his hospitalization, he had an episode of mild encephalopathy. Repeated EEG showed theta slowing of the background with no focal slowing or epileptiform activity. The patient's blood culture was found to be positive, and due to concern for infection, plasmapheresis was discontinued. The patient completed a total of four treatments with minimal improvement. He was discharged then to an inpatient rehabilitation (IPR).

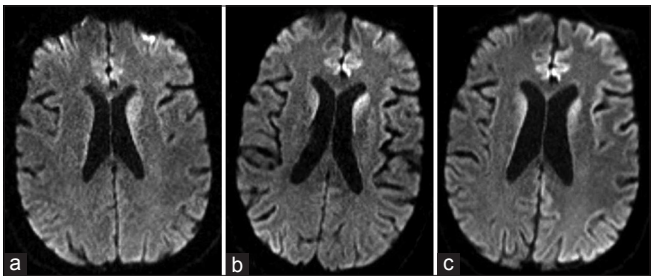

Figure 1: (a) Diffuse-weighted imaging images of patient's first magnetic resonance imaging was read as normal. However, on review, there is some restricted diffusion located in the left caudate and the cortical medial frontal lobes. (b) Diffuse-weighted imaging images on magnetic resonance imaging done 3 weeks after the first magnetic resonance imaging was read as restricted diffusion in the left putamen and left caudate greater than the right caudate, as well as restricted diffusion in the cortex primarily in the left frontal lobe concerning for Creutzfeldt–Jakob disease. (c) The last magnetic resonance imaging done 1.5 weeks after the last one showing the further progression of the restricted diffusion involving the cortex of the left parietal area

While at the IPR, his ophthalmoplegia worsened; he became severely dysarthric, and his mental status began to rapidly decline, which prompted readmission to the hospital. MRI was repeated and showed asymmetric restricted diffusion at the left caudate and anterior left putamen with mild cortical involvement in the left cerebral hemisphere (cortical ribboning pattern) [Figure 1b]. These findings were highly suggestive of CJD.

His examination was significant for substantial cognitive impairment, severe dysarthria, and both vertical and horizontal gaze ophthalmoplegia. He was noted to have ataxia and diffuse rigidity in all extremities. Myoclonus was noted to be absent. Repeated CSF studies revealed positive 14-3-3 proteins, positive real-time quaking-induced conversion assay (RT-QuIC), and total-tau (t-tau) protein with a level of 5243 pg/ml (normal range 0–1149) [Figure 2]. Based on the results, the estimated probability of prion disease, CJD in this case, was deemed >98%. Follow-up EEG study revealed diffuse slowing with occasional triphasic waves. However, the characteristic periodic sharp discharges classically described in CJD were not present [Figure 3].

Test Name	Result	Reference Range for Non-Prion Disease
RT-QuIC (CSF)	Positive	Negative
T- tau protein (CSF)	5243 pg/ml	0-1149 pg/ml
14-3-3 protein (CSF)	Positive	Negative

Figure 2: Cerebrospinal fluid analysis for estimated probability of prion disease. The real-time quaking-induced conversion assay has very high sensitivity and specificity for prion diseases

The patent continued to decline. He had a repeated MRI, which showed the further progression of the restricted diffusion signal abnormality [Figure 1c]. He passed away approximately 14 weeks after his initial presentation to the neurologist. Genetic testing and autopsy were declined by his family.

CONCLUSION

We present a case of CJD that initially presented with peripheral neuropathy and ophthalmoparesis that posed a diagnostic challenge to the treating neurologists. Initially, the patient was treated as possible Miller Fisher variant of GBS, but as the patient progressed and developed rapidly progressive dementia, the diagnosis became more apparent. There have been a few cases reported with sporadic CJD that presented initially with peripheral neuropathy and ophthalmoparesis similar to our case. To the best of our knowledge, familial CJD has not been reported to present with peripheral neuropathy. Our case could represent a sporadic CJD with an unusual presentation or be the first case reported of familial CJD presenting with peripheral neuropathy. Unfortunately, due to the lack of genetic study, we are not able to have a final conclusion.

This case highlights the varied presentation that is seen in CJD and the diagnostic difficulties that it presents. Despite the availability of multiple diagnostic tools to diagnose CJD such as the unique findings on brain MRI and the characteristic EEG findings, these tests may be normal in the early stages of the illness. Testing CSF for 14-3-3 protein, t-tau, and RT-QuIC assay has further widened the array of diagnostic tools although the invasive nature of this test is a deterrent in patients where the presentation is atypical and prion disease is not high on the list of the differential.[11,12]

CJD and other prion diseases are incurable disorders; however, timely diagnosis gives the patients and their

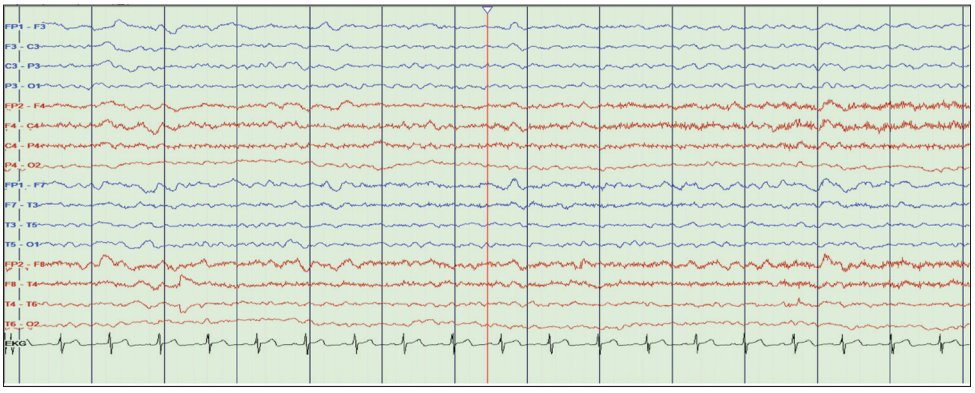

Figure 3: Electroencephalogram of the patient shows diffuse slowing with occasional triphasic waves, lacking periodic sharp waves classically described in Creutzfeldt–Jakob disease

families solace and closure and assists them in determining end-of-life goals. It also avoids subjecting patients to unnecessary treatment modalities, which may prove deleterious to patients. Iatrogenic transmission of prion is a grave concern, and having an accurate early diagnosis might play an important role in taking the necessary precautions while handling the patient's body fluids until further tests are developed that can detect prion diseases in their early stages, the diagnosis would rest on the clinical acumen of physicians and their awareness of heterogeneity of clinical presentations. To underscore the protean manifestations of this disorder, we highlight a case of CJD where painful peripheral neuropathy and ophthalmoparesis heralded the rapid cognitive decline that is typical of this illness.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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