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Case Report

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Brownell-Oppenheimer
Variant of Sporadic
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Unusual Phenotype of the Brownell-Oppenheimer Variant of Sporadic Creutzfeldt-Jakob Disease

Dronacharya Lamichhane

Department of Neurology, University of Iowa Hospitals and Clinics (UIHC), 2RCP, Iowa City, IA 52242, USA.

Correspondence: dronacharya-lamichhane@uiowa.edu

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Abstract

Creutzfeldt-Jakob disease is a rare, transmissible, neurodegenerative disease caused by conformationally changed abnormal prion protein. Most patients present with cognitive impairment, myoclonus, ataxia, visual impairment alone or in combination. Patients who present with ataxia only at the onset are said to have Brownell-Oppenheimer variant of the disease. However, here we present a case where visual symptoms preceded the clinical presentation and hallucinations accompanied the ataxia at the onset of the disease.

Keywords: Ataxia; Creutzfeldt-Jakob disease; Hallucinations; Diplopia.

1. CASE PRESENTATION

A 76-year-old female presented to us with progressive deterioration in walking and frequent falls for approximately 2 months. She already needed a cane or walker for assistance. She was said to be in her usual state of health 2 months ago when she enjoyed independence in all activities of daily living. She had past medical history of rheumatoid arthritis, which was being treated, with infliximab infusion along with methotrexate. She never smoked or abused alcohol. She had family history of Alzheimer's disease in her father and breast and colon cancer in her sisters. According to the family, the patient also had visual hallucinations within 1-2 weeks of noticing difficulty walking. She was reported to seeing firmed imagery like rats running in her house, snake in the living room, and various objects flying off by her.

At this point in time, she was admitted to the hospital for thorough work up. It included magnetic resonance imaging (MRI) brain that was reported to be normal by the neuroradiologist. Electroencephalogram (EEG) revealed normal tracing in awake and drowsy states. Lumbar puncture was obtained that showed mildly elevated protein of 59 mg/dl. Subsequently, the result of extensive investigation, which included a comprehensive paraneoplastic panel as well, to look for a cause of inflammatory processes was negative. Within 2 months from the onset of the first symptom, she started to have rare startle myoclonus. Over the course of 5-6 weeks, she lost 20 pounds of weight and was not able to stand even with a cane leading to having to use a walker. She could no longer ambulate outside the assisted living facility.

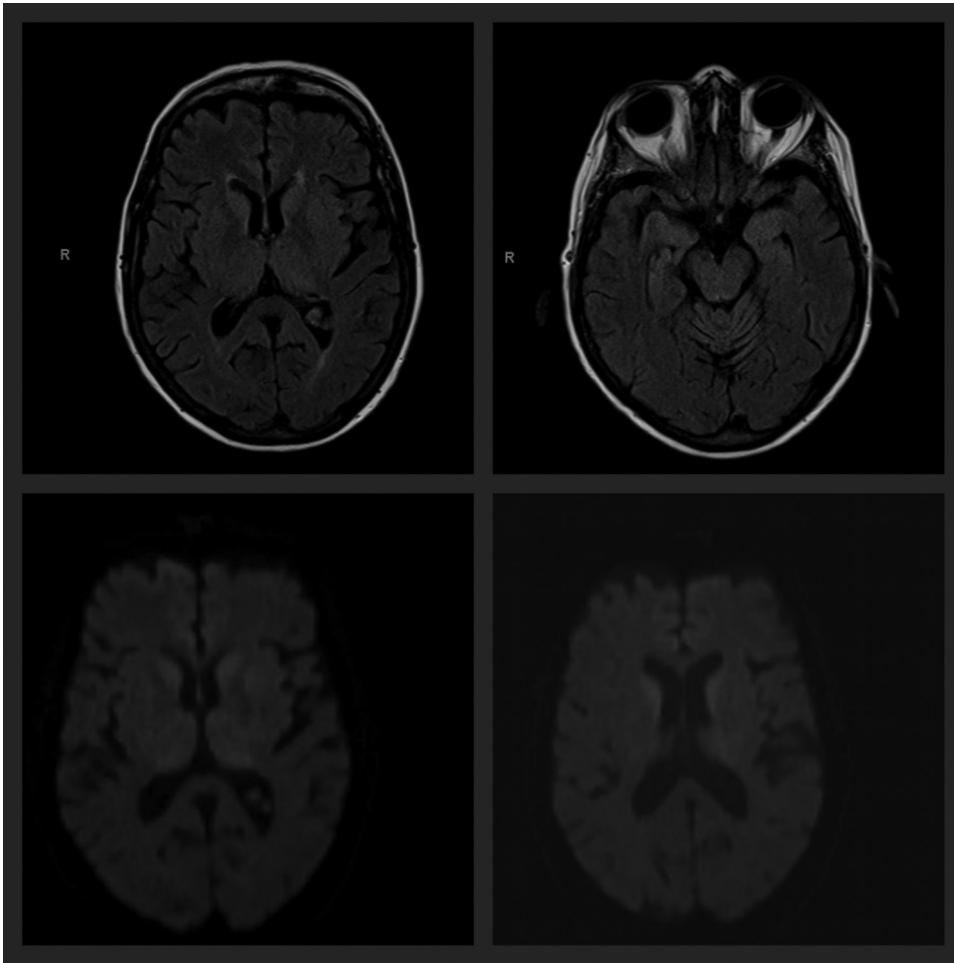
Later in the course of illness, she appeared to have memory disturbances and problems with attention. She also complained of occasional diplopia. Slow vertical and horizontal saccades, divergence insufficiency, and impaired pursuit movements were observed in ophthalmologic evaluation. Interestingly, she had seen an optometrist for double vision, a month before anyone even noticed a problem with her gait, when her regular glasses were changed. Speech was slightly dysarthric. Also, her finger-to-nose test results revealed dyssynergia bilaterally. When we first saw the patient, she was not able to stand up and needed the assistance of two persons to shift herself from the chair to the bed. Lumbar puncture and MRI brain was repeated. 14-3-3 protein was elevated at 7.9 ng/ml (reference range for the lab being <1.2 ng/ml). Unfortunately, the test for beta-amyloid and tau had an inadvertent technical issue. MRI at this time showed restricted diffusion in the bilateral basal ganglia (caudate and putamen), thalami, and insular cortex (Figure 1). EEG obtained this time showed mild to moderate diffuse slowing but no periodic sharp waves or epileptiform discharges. As the patient was wheelchair bound, she was transferred to the nursing home. She died 5 months after the onset of the first symptoms.

Immunohistochemical analysis on the autopsy tissues processed by the Center for Disease Control (CDC) demonstrated abnormal prion protein (PrP) consistent with the prion disease. Sequencing of the PrP revealed type 2 protein. Gene sequencing, to rule out pathogenic mutation in prion protein gene (PRNP), was negative, hence ruling out the familial nature of the disease. Therefore, it was determined that this patient had prion disease with characteristics of sporadic Creutzfeldt-Jakob disease VV2 (sCJD VV2).

2. DISCUSSION

Creutzfeldt-Jakob disease (CJD) is a uniformly fatal disease caused by conformational change of a normally occurring endogenous protein, prion-related protein (PrP^C), into a pathogenic entity (PrP^{Sc}). Depending on how this abnormal protein PrP^{Sc} is

Figure 1: The FLAIR sequences (upper two) of the MRI brain show hyperintensity in the basal ganglia, thalami, insular cortex, cingulate cortices, and medial temporal lobes. The diffusion sequences (lower two) also show the hyperintense signals in the corresponding areas but the signal intensity is somewhat lower.



generated, there are three subtypes of CJD: 1. Sporadic CJD, 2. Familial CJD, and 3. Variant CJD. Familial CJD results because of the mutation of prion protein (PRNP) gene that is inheritable. Variant CJD, which is the rarest subtype, is a truly infectious disease caused by the transmission of the PrP^{Sc} from animals or human to human. Sporadic CJD (sCJD) is the most common form. Although what triggers conversion of normal PrP^c into PrP^{Sc} is not definitely understood; stochastic change in PrP^c or very rare somatic mutation that converts PrP^c to PrP^{Sc} is thought to initiate the cascade of abnormal protein aggregation which is toxic to the neurons [1]. PrP^{Sc} once made perpetuates the process by itself with a positive feedback on the conversion step. sCJD presents with many clinical phenotypes, which in turn, are determined by the genetic makeup of the abnormal protein and the type of protease-resistant prion. Five different clinical variants of sCJD have been classified [2]: 1. Heidenhain variant: visual impairments are the presenting symptoms. 2. Oppenheimer-Brownell variant: ataxia is the presenting sign. 3. Affective variant: neuropsychiatric symptoms are prominent at presentation. 4. Cognitive: cognitive impairment at presentation in the absence of other symptoms and signs. 5. Classic CJD: presenting with cognitive symptoms and ataxia. Cases reported to have symptoms of depression, anxiety, and mood disorders within the first week of illness were classified as having the affective variant if they did not meet inclusion criteria for the Heidenhain group.

Here, we describe a case that presented with cerebellar ataxia, but it was accompanied by visual hallucinations at the outset. Interestingly, her visual symptoms, namely diplopia, preceded the clinical presentation by almost 1 month. MRI brain had significant involvement of the insular and cingulate cortices. Rather, she had extensive involvement of the subcortical structures like basal ganglia and cerebellum. MRI changes were mostly recognizable in diffusion weighted (DWI) and FLAIR sequences [3]. Other features like truncal and appendicular ataxia, progressive dementia, startle myoclonus, and negative EEG findings are consistent with what has been described for ataxia onset sCJD VV2 variant. Diagnosis of CJD was somewhat late because of the absence of cognitive symptoms at presentation and much less subtle MRI findings in the first imaging. Distinct imaging abnormalities were clearly visualized only in the second MRI later in the disease course.

Although diplopia has been described in typical Brown-Oppenheimer variant of the disease, there has been no report of it being present before the onset of all other symptoms of the disease. Only one out of 29 ataxia onset patients had diplopia in one series of 618 patients from the UK [4]. In this series, 5% of the patients had Oppenheim's variant. In another series of 584 patients from the UK, about 2.7% had Heidenhain variant of CJD that presented with isolated visual symptoms. None of them complained of diplopia, though [5]. Most commonly, visual symptoms occur in the context of already known cognitive symptoms, cerebellar ataxia, and abnormal movements. Therefore, it is important that ophthalmologists are aware of the condition, although the condition itself is rare, even more so because any surgical procedure in the eyes carries the risk of iatrogenic transmission of the disease.

In the same series of patients described by Cooper *et al.* [4] from the UK, only about 5% presented with isolated cerebellar signs and symptoms in the absence of other features of the disease. Cerebellar features occur as often as 42-88% of the sCJD cases at any time during the course of illness [6]. Ataxia is the second-most common presenting symptom of CJD only after memory loss. In the early stages, the differential diagnoses are varied because of the absence of the over cognitive problems. The case becomes even more difficult when the EEG and imaging are inconclusive. One of the very interesting features of our case is that the patient was having firm visual hallucinations of first animals and then later different objects in the presence of intact cognition. Visual hallucination, more often ill-defined visual distortion, is another clinical feature of Heidenhain's variant.

According to the molecular classification of sCJD proposed by Parchi *et al.*, sCJD VV2 is the second-most common molecular type (16%) [7]. They concluded that patients in this category presented with cerebellar symptoms, especially at the beginning of the illness. Our case is consistent with this classification but differed in many other clinical presentations as described above. As it can be predicted in VV2 cases, there were no specific EEG findings in our case. The most sensitive test for VV2 variant has been said to be CSF protein 14-3-3 with sensitivity of 95%. Only 12% of patients in this group would have classically described periodic sharp waves in EEG [8]. No single test is solely diagnostic of CJD. The time point at which the investigation is undertaken during a patient's illness does not alter a test's value. Combination of the tests increases sensitivity and specificity of the diagnosis. Most commonly utilized methods of diagnosing CJD in addition to clinical picture are MRI brain, EEG, and CSF. MRI findings are said to be equivalent to elevated levels of 14-3-3 proteins or periodic, sharp, and slow wave complexes in the EEG for the clinical diagnosis of probable sCJD [9]. In one study, DWI and FLAIR imaging was 91% sensitive and 95% specific [10]. Assay of CSF protein 14-3-3 is only moderately accurate in diagnosing sCJD: sensitivity 92% and specificity 80% [11]. 14-3-3 protein along with elevated Tau and neuron-specific enolase (NSE) help identify slightly more cases. Modified WHO criteria that do not use imaging findings require tissue biopsy for definite diagnosis of CJD [12]. European MRI-CJD Consortium has proposed a set of criteria that utilizes MRI findings also, increasing the sensitivity but affecting the specificity only marginally [9].

There is no definitive treatment of CJD as is the case with other neurodegenerative diseases. A few trials with doxycycline, flupirtine, and quinacrine in CJD failed to prolong life expectancy or improve memory [13]. Curcumin, an ingredient naturally found in food spice turmeric, has shown a promise in the realm of treatment of CJD. This compound can inhibit inflammation and reduce α -amyloid aggregation in animals. Curcumin inhibits conversion of PrP^C into β -PrP^{Sc} by binding to α -helical intermediate [14]. Certainly, more research is warranted on this compound, which has a longstanding history of minimal toxicity as evident by its use in Indian subcontinent as a food spice for several 100 years.

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Conflict of Interest

None.

References

1. Weissmann C, Enari M, Klöhn P-C, Rossia D, Flechsig E. Transmission of prions. *Proc Natl Acad Sci U S A*. 2002; 99(Suppl 4):16378-83. doi:10.1073/pnas.172403799
2. Appleby BS, Appleby KK, Crain BJ, Onyike CU, Wallin MT, *et al.* Characteristics of established and proposed sporadic Creutzfeldt-Jakob disease variants. *Arch Neurol*. 2009; 66(2):208-15. doi:10.1001/archneurol.2008.533
3. Meissner B, Kallenberg K, Sanchez-Juan P, Collie D, Summers DM, *et al.* MRI lesion profiles in sporadic Creutzfeldt-Jakob disease. *Neurology*. 2009; 72(23):1994-2001. doi:10.1212/WNL.0b013e3181a96e5d
4. Cooper SA, Murray KL, Heath CA, Will RG, Knight RSG. Sporadic Creutzfeldt-Jakob disease with cerebellar ataxia at onset in the UK. *J Neurol Neurosurg Psychiatry*. 2006; 77(11):1273-75. doi:10.1136/jnnp.2006.088930
5. Cooper SA. Isolated visual symptoms at onset in sporadic Creutzfeldt-Jakob disease: The clinical phenotype of the 'Heidenhain Variant'. *Br J Ophthalmol*. 2005; 89(10):1341-42. doi:10.1136/bjo.2005.074856
6. Will RG, Matthews WB. A retrospective study of Creutzfeldt-Jakob disease in England and Wales, 1970-79. I: Clinical features. *J Neurol Neurosurg Psychiatry*. 1984; 47(2):134-40.
7. Parchi P, Giese A, Capellari S, Brown P, Schulz-Schaeffer W, *et al.* Classification of sporadic Creutzfeldt-Jakob disease based on molecular and phenotypic analysis of 300 subjects. *Ann Neurol*. 1999; 46(2):224-33.

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8. Collins SJ, Sanchez-Juan P, Masters CL, Klug GM, van Duijn C, *et al.* Determinants of diagnostic investigation sensitivities across the clinical spectrum of sporadic Creutzfeldt-Jakob disease. *Brain J Neurol.* 2006; 129(Pt 9):2278-87. doi:10.1093/brain/awl159
9. Zerr I, Kallenberg K, Summers DM, Romero C, Taratuto A, *et al.* Updated clinical diagnostic criteria for sporadic Creutzfeldt-Jakob disease. *Brain.* 2009; 132(10):2659-68. doi:10.1093/brain/awp191
10. Young GS, Geschwind MD, Fischbein NJ, Martindale JL, Henry RG, *et al.* Diffusion-weighted and fluid-attenuated inversion recovery imaging in Creutzfeldt-Jakob disease: High sensitivity and specificity for diagnosis. *Am J Neuroradiol.* 2005; 26(6):1551-62.
11. Muayqil T, Gronseth G, Camicioli R. Evidence-based guideline: Diagnostic accuracy of CSF 14-3-3 protein in sporadic Creutzfeldt-Jakob Disease Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2012; 79(14):1499-506. doi:10.1212/WNL.0b013e31826d5fc3
12. WHO Global Surveillance, Diagnosis and Therapy of Human Transmissible Spongiform Encephalopathies: Report of a WHO Consultation. Geneva, Switzerland, February 9-11, 1998. http://www.who.int/csr/resources/publications/bse/WHO EMC_ZDI_98_9/en/
13. Geschwind MD, Kuo AL, Wong KS, Haman A, Devereux G, *et al.* Quinacrine treatment trial for sporadic Creutzfeldt-Jakob disease. *Neurology.* 2013; 81(23):2015-23. doi:10.1212/WNL.0b013e3182a9f3b4
14. Hafner-Bratkovič I, Gašperšič J, Šmid LM, Bresjanac M, Jerala R. Curcumin binds to the A-helical intermediate and to the amyloid form of prion protein – a new mechanism for the inhibition of PrP^{Sc} accumulation. *J Neurochem.* 2008; 104(6):1553-64. doi:10.1111/j.1471-4159.2007.05105.x

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