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Precipitous Deterioration of Motor Function, Cognition, and Behavior

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Abstract

A 72-year-old woman developed new-onset depression, sustained an unexplained fall, and started walking cautiously. After 1 year, her depression resolved but she developed a dry cough. One year later, she experienced a more rapid decline in her gait with parkinsonism, visual difficulties with restricted vertical gaze, slowed horizontal and vertical saccades, dysphagia, apathy, and progressive cognitive decline, which led to her death 2 years later. The differential diagnosis, neuroimaging, and pathological findings are discussed, as well as their public health implications.

Report of a Case

Following her son's death, a 72-year-old woman with a history of hypertension and hypothyroidism developed a year of severe depression, fell and broke her arm, and walked cautiously while dragging her right leg. A year later, she developed an unexplained dry

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cough and hoarseness. Two years after her initial fall, she complained of weakness and developed gait instability, needing to hold on to something when walking (“onset”). From this point, her deterioration was quick and included a sense of leg weakness, “not seeing well,” and pronounced apathy. Seven months after “onset,” an examination revealed symmetrical hyperreflexia with a jaw jerk and an overactive gag reflex but was otherwise normal, failing to identify weakness or gait unsteadiness. Between months 7 and 13, she was dizzy when turning without experiencing vertigo, and began losing her balance, falling twice. At 14 months, she needed a cane and could not concentrate or manage her checkbook, but she was oriented to the date, had a knowledge of recent events, and had a 3 of 3 one-minute recall.

During months 14 through 16 she became more apathetic and depressed, had intermittent memory and orientation problems, worsening parkinsonism (bradykinesia, difficulty initiating movement, micrographia, emerging tremor, and intermittently needing a wheelchair) without ataxia, and favored her left leg when walking. By month 17 her apathy increased, and she occasionally dragged her right foot. On examination, she was alert and oriented to the month and year, had intact naming, and a normal cranial nerve examination, but she was intermittently tearful, had impaired spontaneous word generation and recall, mild hypomimia, mildly slowed bilateral rapid movements, retropulsion on standing, collapse on sitting, and normal stride only with assistance. She did, however, have normal strength, tone, sensation, reflexes, and plantar flexor responses without dysmetria.

At 19 months, she had dysphagia, dysarthria, word-finding problems, difficulty turning in bed, and leg movements and talking during sleep. Carbidopa-levodopa failed to improve symptoms. A neurological examination also revealed a blunted affect, a 10 of 25 Montreal Cognitive Assessment score, mild hypomimia, right gaze diplopia, an impaired upgaze, moderately slowed rapid alternating movements, a bilateral pronator drift, extreme micrographia, and generalized parkinsonism, requiring assistance to rise from a chair and walk.

At her first visit to the University of California, San Francisco Memory and Aging Center at 21 months, her family reported her intermittent word comprehension difficulty, paraphasias, pseudobulbar affect, and progressive myoclonus. Her examination showed distractibility, severe hypomimia, moderate hypophonia, slowed eyelid opening, a restricted vertical gaze, slowed horizontal and vertical saccades, a saccadic horizontal pursuit, marked axial and limb rigidity, extreme and predominantly right-sided bradykinesia, postural tremor, myoclonus, a marked grasp reflex, brisk reflexes, and upgoing plantar responses. Cognitive testing results revealed a Mini-Mental State Examination score of 7 of 30, severe memory impairment, an inability to copy a complex (the Benson) figure, and very impaired frontal-executive function and working memory. By 27 months, she had declined dramatically, experiencing sleepiness, intermittent eye opening, an inability to follow simple commands, mutism, and flexed, contracted, and spastic extremities. She died 28 months after “onset,” with a possible disease course of more than 4 years.

Laboratory and Neuroradiological Data

Extensive laboratory testing for dementia, including ceruloplasmin and serum/urine copper, yielded normal results. The patient's traumatic lumbar puncture at 27 months showed a mildly elevated protein level (white blood cell count, 1; red blood cell count, 985; protein, 53 mg/dL [normal = 0–50 mg/dL]; glucose, 63 mg/dL).

Magnetic resonance imaging (MRI) at month 14 (Figure 1A and C) reported mild atrophy and "mild altered signal intensities in sublenticular white matter and basal ganglia, including caudate head, minutely increased on T1- and T2-weighted sequences," which "may reflect underlying pigment/mineral deposition." Magnetic resonance imaging at month 20 (Figure 1B and D) reported mild atrophy and mild small vessel disease. There was no change in the slight bilateral striatal T2-weighted hyperintensity.

Clinical Discussion (Dr Perry)

This patient's clinical course is characterized by an uncertain time of onset, with 2 years of nonprogressive, potentially related symptoms, including depression, a single fall, and dry cough with hoarseness. This was followed by a progressive neurological decline over 2 years involving multiple systems, with evidence of extrapyramidal, pyramidal, oculomotor, cognitive, and behavioral features. In evaluating patients who present late in their course with the involvement of multiple neurological systems and significant impairment, it is helpful to revisit the first symptoms, as neurodegenerative diseases often begin preferentially in a small number of regions. With the addition of more symptoms and an understanding of the progression rate, the clinician attempts to recognize known syndromes and looks for individual features with sufficient specificity to narrow the diagnostic possibilities. This patient's first symptoms were nonspecific. Depression can be the first manifestation of many neurodegenerative diseases. The presence of extrapyramidal, myoclonic, cognitive, and behavioral features suggests a more limited set of possibilities, with dementia with Lewy bodies being the most common. She had features, however, that made this unlikely, including eye movement abnormalities and early falls, which may indicate progressive supranuclear palsy (PSP). She met the diagnostic inclusion criteria for probable PSP, including an age of 40 years or older at onset, progressive disorder with early vertical supranuclear gaze palsy, and prominent postural instability with falls in the first year of onset. She also met supportive criteria, including symmetric akinesia, levodopa nonresponsive parkinsonism, early cognitive impairment, apathy, and dysphagia.[1] The MRI striatal hyperintensity, downplayed by the radiological interpretation, however, might qualify as a relevant basal ganglia "structural" abnormality, which is an exclusion criterion for a PSP diagnosis.[1] In addition, some of the patient's other features were atypical for PSP, including myoclonus, asymmetry, and no axial rigidity. Her disease duration was shorter than the average 5 to 7 years seen in PSP, although more rapid cases have been described.[2]

Corticobasal degeneration could also explain the patient's atypical parkinsonism, lack of levodopa responsiveness, myoclonus, and cognitive and behavioral features, but it would not be expected to cause her oculomotor findings until a late stage. Saccadic eye movement abnormalities have also been described in motor neuron disease (she had no lower motor

neuron findings), multiple system atrophy, and spinocerebellar ataxia (she had no family history or cerebellar findings). A PSP syndrome has been described with some *DCTN1* mutations, but again, she lacked a relevant family history. Vertical supranuclear gaze palsy, movement disorders, and cognitive and psychiatric symptoms are seen in late-onset Niemann-Pick C disease, though what is considered late for that illness would still be much earlier than this patient's age at onset. Wilson disease rarely occurs after age 70 years and can cause vertical eye movement abnormalities and parkinsonism, but she had negative copper and ceruloplasmin test results, making this less likely. Whipple disease can cause parkinsonism and vertical ophthalmoplegia, and though she had no gastrointestinal symptoms, a minority of cases have isolated central nervous system involvement.

Her MRI most strongly raises concern for prion disease, with striatal and cingulate hyperintensities more prominent on diffusion-weighted-imaging than on fluid-attenuated inversion recovery.[3] Restricted diffusion in the striatum and cortex (cortical ribboning) on diffusion-weighted imaging is among the most sensitive and specific antemortem tests for detecting Jakob-Creutzfeldt Disease (JCD) with a diagnostic accuracy of 97%.[3] A 4-year time course would be longer than expected for JCD, and vertical gaze palsy with slowed saccadic velocity is not typically described. Prion disease, however, can present in numerous ways[4] and would explain her relatively rapid progression, myoclonus, parkinsonism, and cognitive impairment.

Neuropathological Discussion (Drs Grinberg and DeArmond)

A brain pathological assessment was performed at the University of California, San Francisco/Memory and Aging Center Neurodegenerative Disease Brain Bank and the National Prion Disease Pathology Surveillance Center. Postmortem delay was 12 hours and the brain weighed 1079 g. A gross examination revealed general atrophy and ventriculomegaly with substantia nigra pigment loss, mildly thinned cortical ribbon, and a normal size midbrain. Microscopy showed extensive cortical vacuolation prominent in the deep layers, with colocalized astrogliosis and neuronal loss. Vacuolation also involved striatum and dentate nucleus of the cerebellum, but was mild in the hippocampus and was not present in the occipital cortex and cerebellar molecular layer. The substantia nigra showed a moderate loss of neuromelanin. β-Amyloid and phospho-tau immunostaining revealed low Alzheimer disease neuropathologic changes (National Institute on Aging–Alzheimer's Association A1B1C0). Transactive response deoxyribonucleic acid binding protein- 43 (ie, TDP-43) and fused in sarcoma (ie, FUS) staining were negative.

Immunostaining using the anti-prion protein (PrP) antibody 3F4 showed diffuse or "synaptic" PrP^{Sc} in most brain regions and no plaques. Molecular and genetic analyses showed type 1 prion, no mutation in the prion protein gene, and codon 129 polymorphism methionine-valine (ie, sJCDMV1) subtype[5] but with atypical predominance of unglycosylated PK-resistant PrP^{Sc} (US National Prion Disease Pathology Surveillance Center) (Figure 2). Interestingly, her cerebrospinal fluid research test results, which returned post mortem, revealed normal total and phospho-tau levels, but novel biomarkers (N-terminal and central epitopes of the tau protein [BT2 + HT7; HT7 + Tau5]) as well as the

neurofilament light chain were 9 to 19 times higher than typical forPSP,[6,7] which additionally would have suggested against a PSP diagnosis.

Conclusions

Although classical sporadic JCD (sJCD) involves rapid dementia with ataxia and myoclonus, sJCD has a variable semiology and duration[3] and is commonly misdiagnosed.[4] A recent study showed that sJCD patients had almost 4 misdiagnoses before correctly being diagnosed, including atypical parkinsonian syndromes (4%), but none with PSP.[4] Although the initial criteria for "probable PSP" were reported to have a sensitivity of 83% and specificity of 100%, both seem lower in clinical practice.[8] In the literature, 12 prion cases mimicking PSP have been previously reported, with 5 having a long duration (29–53 months). To our knowledge, this is the first case of a patient with sJCD MV1 fulfilling probable PSP criteria.[1]

The median life expectancy for patients is about 5 months in the sJCDMV1 subtype, but with a wide range (1–54 months).[9] Most other sJCD subtypes have median durations of about 1 year, with similarly large ranges.[9] In this patient, it was difficult to determine the onset of symptoms because she was relatively stable for 2 years after her first fall, but her disease duration was at least 28 months from the onset of progressive neurological decline, which is within the range reported previously.[9]

Besides walking difficulty and instability, eye movement abnormalities can also lead to misdiagnosing JCD as PSP. Unfortunately, most prion disease cohort studies report oculomotor and visual symptoms as a combined category, making it difficult to study the true frequency of each. Oculomotor problems in sJCD and genetic prion disease have been reported, however, in case reports.[10] In this case, early vision complaints but late oculomotor problems could be consistent with JCD.[10] The late oculomotor problems were not as consistent with PSP, however.[1,8]

Ancillary test results might have been useful to diagnose JCD. The patient's 14-month sagittal MRIs suggested rostral midbrain atrophy, a signal sometimes helpful in differentiating PSP from PD or multiple system atrophy,[11] but the striatal and subtle diffusion-weighted imaging cortical ribboning hyperintensities should have raised suspicion for JCD. Unfortunately, sJCD MRIs are often misread.[3] Cerebrospinal fluid proteins (14-3-3, neuron-specific enolase, and total-tau) have moderate diagnostic utility, although their absence does not exclude JCD.[3] An electroencephalogram, particularly in later stages, might have revealed periodic sharp wave complexes suggestive of JCD.[3] In retrospect, she met World Health Organization 1998 clinical criteria for possible sJCD, which require symptoms but not ancillary tests (required for probable sJCD), which were never performed.[3] She met European 2009 and University of California, San Francisco criteria[3] for probable sJCD, due to her abnormal diffusion-weighted imaging MRI.

A neuropathological examination showed JCD-like features atypical for the sJCD MV1 subtype, in which vacuolation and PrP^{Sc} deposition usually involves all cerebral cortex layers plus neostriatum, thalamus, and cerebellum, sparing hippocampus and brainstem

nuclei.[5] In this case, vacuolation showed a laminar pattern affecting mostly the inner cortical layers. Moreover, the midbrain was severely involved and the molecular layer of the cerebellum and occipital cortex were spared, unlike sJCDMV1. The substantia nigra involvement explains the profound parkinsonism. Some of the histopathological features of this case are reminiscent of sJCD MV2 and VV2 subtypes, although PrP^{Sc} plaques are missing.[5] A Western blot showed PrP^{Sc} type 1, but with an atypical ratio of di, mono, and unglycosylated PrP^{Sc} isoforms that was at variance with sJCDMV1 subtype (as well as other sJCD subtypes)[5] and resembling an atypical PrP^{Sc} prior case report.[12]

Sporadic JCD, even MV1 subtypes, can have clinically atypical presentations, including PSP-like presentations, with a disease duration of more than 2 years. In this case, the presence of myoclonus, asymmetric features, a relatively rapid course, and the MRI findings should have suggested against PSP and raised suspicion for JCD. Had her MRI been interpreted properly, she might have been diagnosed correctly ante mortem. A careful read of a diffusion-weighted imaging/apparent diffusion coefficient MRI is essential in cases of atypical neurodegenerative diseases, particularly with unusually rapid presentations. In this case, cerebrospinal fluid was distributed to several research centers, and most disturbingly, the neuropathology laboratory personnel and equipment were unnecessarily exposed to PrP^{Sc}. An early and accurate diagnosis of sJCD is extremely important for infection control and prognostic reasons.

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Conflict of Interest Disclosures

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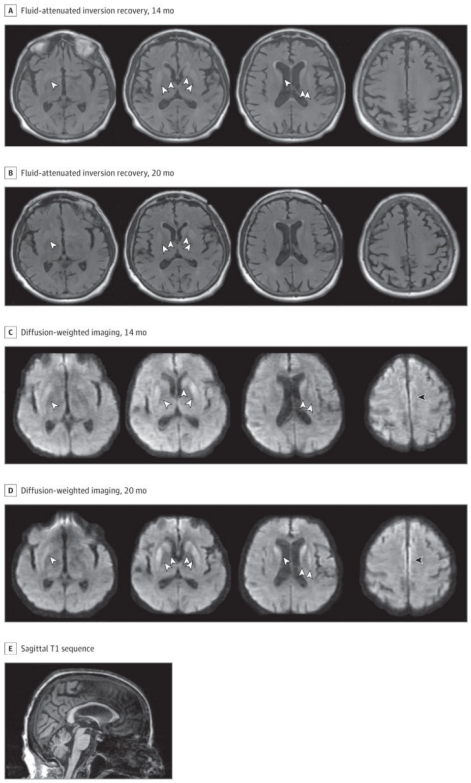

Figure 1. Brain Magnetic Resonance Imaging

Fluid-attenuated inversion recovery (A and B) and diffusion-weighted imaging (C and D) sequences at 14 (A and C) and 20 months (B and D), respectively, showing striatal (white arrowheads) and midcingulate cortical ribboning (black arrowhead) hyperintensities consistent with prion disease. Note that the abnormalities are identified more easily on diffusion-weighted imaging than fluid-attenuated inversion recovery sequences. The sagittal T1 sequence (E) shows a possible hummingbird sign with an atrophied midbrain compared with the pons, which some investigators feel is a helpful, distinguishing feature of progressive supranuclear palsy vs idiopathic Parkinson disease and other parkinsonian disorders.

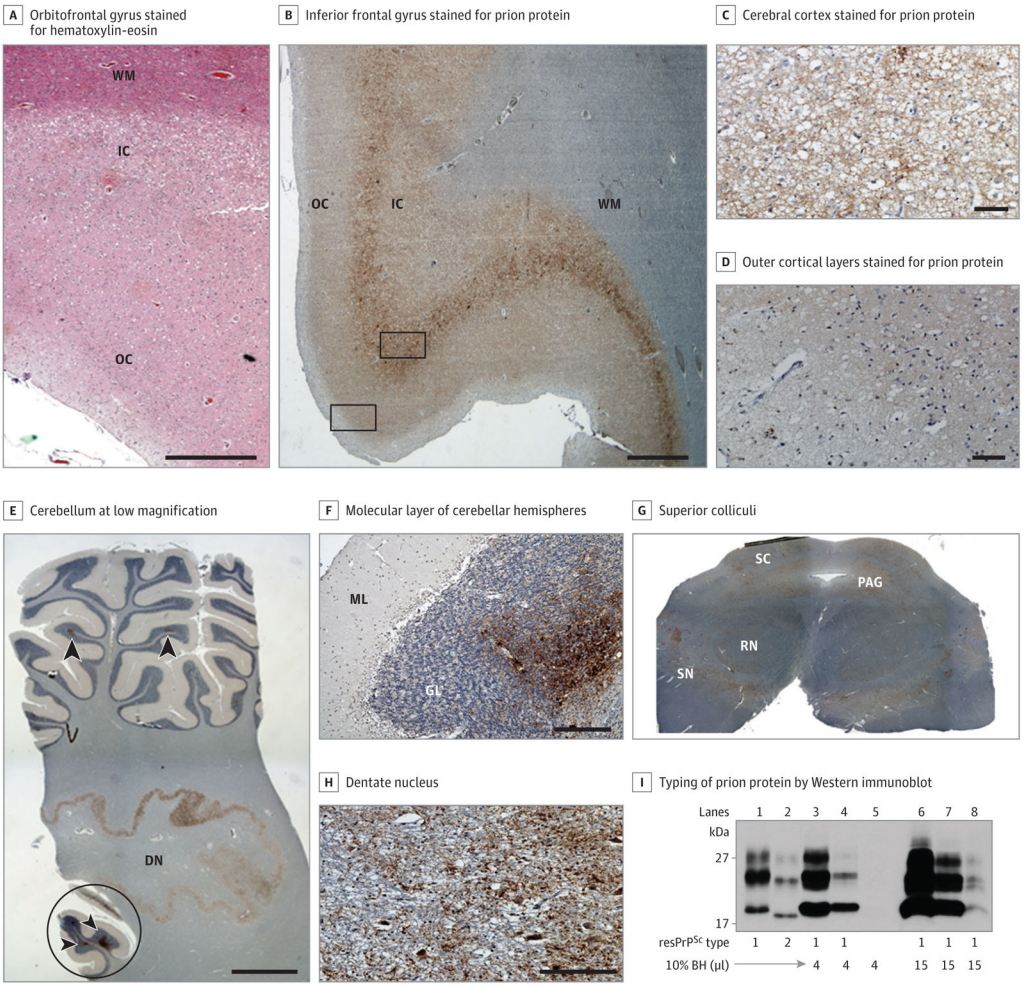

Figure 2. Pathological Findings: Histopathology and Prion-Related Protein Scrapie (PrP^{Sc})Western Immunoblot

A, Orbitofrontal gyrus stained for hematoxylin-eosin. Vacuolation affects predominantly the inner cortical layers. B–H, Immunohistochemistry. B, Inferior frontal gyrus immunostained for PrP (3F4). In the cerebral cortex, PrP^{Sc} had a laminar pattern of distribution and stained mainly layers IV–VI (brownish color), magnified in C, and relatively spared the outer cortical layers, magnified in D (black boxes in B show the regions magnified in C and D). E, Cerebellum at low magnification. Prion-related protein scrapie immunostaining with focal distribution (arrowheads) in the cerebellar granular layer is especially intense in the flocculus (circle) (magnified in F). The molecular layer of cerebellar hemispheres did not show PrP^{Sc} immunostaining. Intense PrP^{Sc} immunostaining was also seen in the dentate nucleus (magnified in G) and in the brainstem (including tectum, substantia nigra, dorsal raphe nucleus, and nucleus of the solitary tract; not shown). H, Superior colliculi (tectum), periaqueductal gray, and substantia nigra of midbrain shows abundant PrP^{Sc} deposition. I, Typing of PrP^{Sc} by Western immunoblot. Brain homogenates (BHs) with antibody 3F4 from the present case (lanes 3–8), as well as sCJDMM1 (lane 1) and sCJDMM2 (lane 2) control cases were subjected to digestion with 5 U/mL (corresponding to approximately 100 µg/mL) proteinase K (PK). The unglycosylated (lowest band) PK-resistant PrP^{Sc} ($resPrP^{Sc}$) from the

frontal cortex (lanes 3 and 6), parietal cortex (lanes 4 and 7), and cerebellum (lanes 5 and 8) of the present case co-migrated at approximately 21 kDa with unglycosylated resPrP^{Sc} type 1 associated with sCJDMM1 (lane 1) but not with the ~19 kDa unglycosylated resPrP^{Sc} type 2 of sCJDMM2 (lane 2). Lanes 3 to 5 were rerun with less BH than lanes 6 to 8, and lanes 3 to 4 clearly show the predominance of unglycosylated resPrP^{Sc}, which is atypical for MV1. Scale bars: A, B, and E: 500 μm; C, D, and G: 50 μm; F: 100 μm; H: 1 cm. DN indicates dentate nucleus; GL, granular layer; IC, inner cortical layers; ML, molecular layer; OC, outer cortical layers; PAG, periaqueductal gray; PrPSc, prions; SC, superior colliculus; SN, substantia nigra; u, unglycosylated; WM, white matter.