CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL



# Case 32-2019: A 70-Year-Old Woman with Rapidly Progressive Ataxia

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## PRESENTATION OF CASE

*Dr. Kun-Wei Song* (Neurology): A 70-year-old woman was admitted to this hospital because of rapidly progressive ataxia.

The patient had been in her usual state of good health until 3 months before this admission, when fatigue and general unsteadiness developed. Two months before admission, episodes of worsening unsteadiness occurred. The patient was no longer able to walk in a straight line or to remain stable in yoga poses that had previously been easy for her. No associated falls, vertigo, loss of consciousness, ear pain, hearing loss, tinnitus, or headache were reported. She was evaluated by her primary care physician, who was affiliated with another hospital, and a neurologic examination was reportedly normal. The white-cell count, hematocrit, hemoglobin level, and blood levels of electrolytes, glucose, and thyrotropin were normal, as were the results of kidney-function and liver-function tests; a test for Lyme disease was negative. The patient was referred to an otolaryngologist.

Seven weeks before admission, the patient was evaluated by an otolaryngologist at the other hospital. The examination revealed auditory canals and tympanic membranes that were normal in appearance; an audiogram showed normal hearing. The patient was told that her symptoms were not caused by a vestibular process, and she was referred to a neurologist.

Four weeks before admission, progressive gait imbalance developed. The patient was able to walk in her home without falling by leaning on walls and surfaces for support, but she needed a cane or the assistance of her husband to walk outside. She was evaluated in a neurology clinic at the other hospital. She reported a sensation of impaired balance that persisted when she was seated in a chair and diminished, but did not resolve, when she was in the supine position. She also noted a loss of coordination in her hands; her handwriting had progressively become larger, and she had difficulty eating soup. She reported new blurry vision, insomnia, and a constant mild headache.

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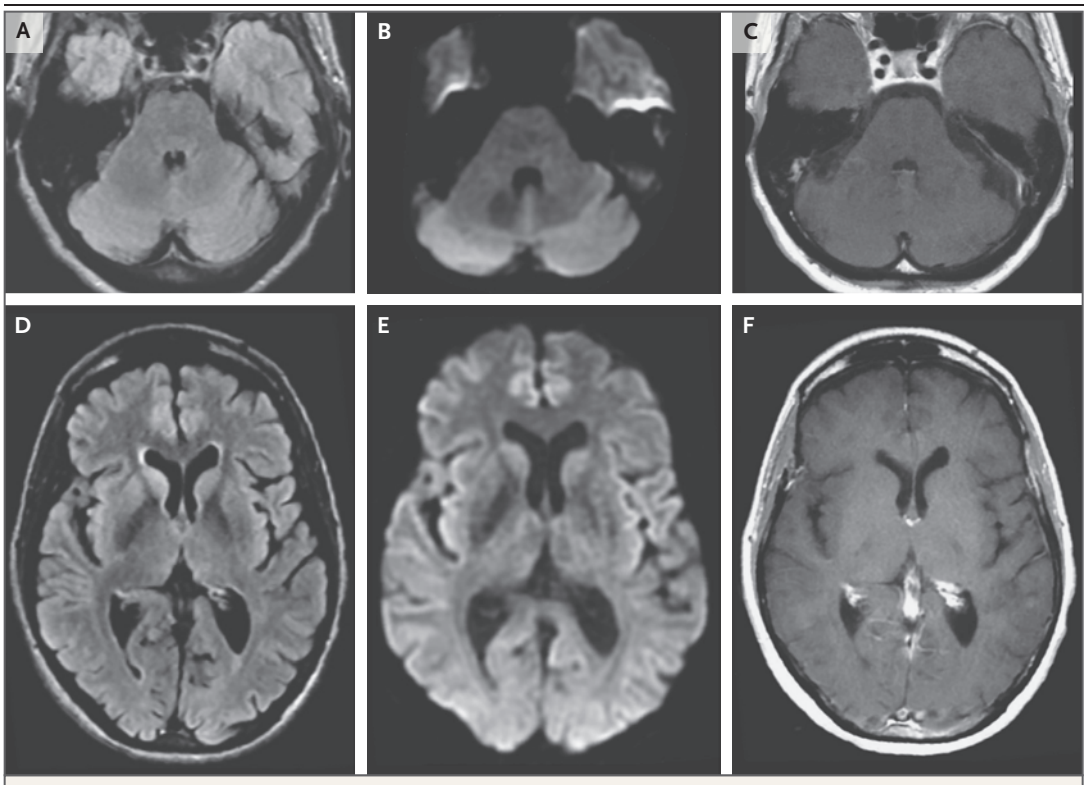


**Figure 1. MRI of the Head Obtained 4 Weeks before the First Admission.**

Axial T2-weighted fluid-attenuated inversion-recovery (FLAIR) images, diffusion-weighted images, and T1-weighted images with contrast enhancement, obtained at the level of the cerebellum (Panels A, B, and C, respectively) and at the level of the basal ganglia (Panels D, E, and F, respectively), show no definite abnormal signal or enhancement.

On examination, the patient was awake, alert, and oriented. Her speech was fluent and clear. A slightly wide-based, unsteady gait was noted, with jerking movements of the trunk, hips, and legs. She was unable to walk with a tandem gait or on her toes or heels. The Romberg sign was present, and a subtle postural tremor in both hands was noted. The remainder of her neurologic examination was normal. Antinuclear antibodies were present at a titer of 1:40 with a speckled pattern. Blood levels of folate, thiamine, cyanocobalamin (vitamin $B_{12}$), vitamin E, vitamin $B_6$, and C-reactive protein were normal, as was the erythrocyte sedimentation rate. Results of serum protein electrophoresis were also normal. A screening test for syphilis was negative.

*Dr. Bradley R. Buchbinder:* Magnetic resonance imaging (MRI) of the head was performed before and after the administration of intravenous contrast material. T2-weighted fluid-attenuated inversion recovery (FLAIR) imaging showed minimal, confluent periventricular signal hyperintensity and scattered focal subcortical signal hyperintensity in both cerebral hemispheres, with mild ventricular prominence (Fig. 1).

*Dr. Song:* The patient was advised to undergo physical therapy for balance training. Two weeks before admission, sudden and involuntary movements of the arms developed that were associated with loss of positional awareness. The patient sought a second opinion from an otolaryngologist at this hospital, who referred her to the emergency department; she was admitted to the neurology service for further evaluation. She reported ongoing involuntary movements of the arms and loss of positional awareness. Her husband reported that she would often place her coffee cup on a table with excessive force or drop it several inches above the surface. She now re-

quired a walker and had had two falls resulting from loss of balance. She also noted new horizontal double vision, decreased appetite, weight loss of approximately 2 to 3 kg in the past month, and a cough.

The patient was right-handed. She had a history of hyperlipidemia, impaired glucose tolerance, and asthma and a long history of mild hearing loss. Medications included simvastatin, vaginal estrogen, and, as needed, lorazepam for insomnia. She had no known medication allergies.

The patient was a retired educator and lived with her husband in New England. She had traveled extensively in the eastern United States and in Western Europe. She had previously participated in daily aerobics, yoga, and dance classes. She had consumed one glass of wine nightly but stopped when her symptoms began. She did not smoke tobacco or use illicit drugs. Her mother had hypertension, and her father had died from lung cancer; her brother and two adult children were healthy. There was no family history of ataxia, dementia, autoimmune disease, or neurodegenerative disease.

On examination, the patient was alert, oriented, and interactive. The temperature was 36.1°C, the pulse 71 beats per minute, the blood pressure 143/94 mm Hg, the respiratory rate 18 breaths per minute, and the oxygen saturation 98% while the patient was breathing ambient air. The neck was supple, and she did not have thyromegaly or thyroid nodules. The speech was fluent, with no dysarthria. She had marked dysmetria bilaterally on finger-to-nose and heel-to-shin testing; severe dysdiadochokinesia (i.e., an impaired ability to perform rapid alternating movements) was also noted. The gait was wide-based and unsteady, with truncal ataxia. The remainder of the examination was normal, including repetition and naming, strength, deep-tendon and plantar reflexes, and sensory function. Blood levels of electrolytes, glucose, arsenic, lead, mercury, and cadmium were normal, as were the results of kidney-function testing and urine toxicologic screening. A lumbar puncture was performed, and tests for paraneoplastic antibodies in the blood and cerebrospinal fluid (CSF) were negative. Other laboratory test results and the results of the CSF analysis are shown in Table 1. An MRI of the head was obtained and was interpreted as unchanged from the study obtained 1 month earlier.

**Table 1. Laboratory Data.***

| Variable | Reference Range, Adults† | On Admission, This Hospital |
|---|---|---|
| **Blood** | | |
| Hemoglobin (g/dl) | 12.0–16.0 | 12.1 |
| Hematocrit (%) | 36.0–46.0 | 37.3 |
| White-cell count (per $mm^3$) | 4500–11,000 | 6390 |
| Differential count (%) | | |
| Neutrophils | 40–70 | 60.6 |
| Lymphocytes | 22–44 | 26.4 |
| Monocytes | 4–11 | 9.7 |
| Eosinophils | 0–8 | 2.3 |
| Basophils | 0–3 | 0.8 |
| Immature granulocytes | 0.0–0.9 | 0.2 |
| Thyrotropin (μIU/ml) | 0.40–5.00 | 4.51 |
| Thyroid peroxidase antibodies (IU/ml) | <9 | 260 |
| Thyroglobulin antibodies (IU/ml) | <4.0 | 29 |
| **Cerebrospinal fluid** | | |
| Color | Colorless | Colorless |
| Turbidity | Clear | Clear |
| Glucose (mg/dl) | 50–75 | 66 |
| Total protein (mg/dl) | 5–55 | 33 |
| Red-cell count (per $mm^3$) | 0–5 | 1 |
| Total nucleated cells (per $mm^3$) | 0–5 | 1 |
| Differential count (%) | | |
| Segmented neutrophils | 0 | 0 |
| Lymphocytes | 0–100 | 59 |
| Monocytes | 0–100 | 41 |
| Xanthochromia | Not present | Not present |

* To convert the values for glucose to millimoles per liter, multiply by 0.05551.
† Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

An electroencephalogram (EEG) showed a single sharp wave in the left parietal region but was otherwise normal. Combined positron-emission tomography and computed tomography (PET-CT) from the skull base to midthigh, performed after the administration of intravenous $^{18}$F-fluorodeoxyglucose (FDG) tracer, revealed no abnormal FDG uptake. A working diagnosis of autoimmune cerebellitis was made, and intrave-

nous immune globulin was administered. The patient was discharged home on the sixth hospital day, with a plan to follow up in the ataxia unit of this hospital.

Three weeks after discharge, the patient was evaluated in the ataxia unit. Her gait and coordination had worsened; she could no longer ambulate independently with a walker and required one-person assistance. New dysarthria had developed, along with short-term memory loss; she began to forget conversations held earlier in the day. Oculomotor examination revealed occasional square-wave jerks in the primary position (i.e., inappropriate saccades that take the eyes off the target when a person is looking forward, followed by a corrective saccade that brings the eyes back to the target), slowed pursuit movements with frequent saccadic intrusions, hypermetric and hypometric saccades, and mild gaze-evoked nystagmus in the horizontal plane. Her dysarthria was mild but became worse when she attempted to recite consonants rapidly. On finger-to-nose testing, there was bilateral end-point dysmetria with oscillating movements at the elbows, overshoot during rapid finger movements, and dysdiadochokinesia. On heel-to-shin testing, the patient had jerking movements of the shins in the axis, with occasional superimposed lateral movements that occurred more frequently on the left side than on the right side. Rapid tapping of the heels on the ground was dysrhythmic. The gait was profoundly impaired; it was wide-based and unstable, and there was marked titubation of the trunk. The patient required maximal one-person assistance. She was unable to spontaneously recall a list of five words learned a few minutes earlier, and her recall did not improve even after she was provided a category clue or a list of multiple-choice answers. Her score on the Montreal Cognitive Assessment was 15 on a scale of 0 to 30, with a score of less than 25 indicating cognitive impairment and lower scores indicating greater cognitive impairment.

The patient was readmitted to the neurology service of this hospital, and a diagnosis was made.

## DIFFERENTIAL DIAGNOSIS

*Dr. Bart K. Chwalisz:* This 70-year-old woman presented with rapidly progressive ataxia — an impairment in the rate, range, and rhythm of voluntary movement that is unexplained by weakness. This condition can result from cerebellar and extracerebellar disease. My first step in constructing a differential diagnosis is to localize the lesion in the nervous system.

### LOCALIZATION

Dysfunction of the somatosensory and vestibular inputs into the cerebellum can cause ataxia, and sensory ataxia typically worsens with removal of visual fixation. This phenomenon is the basis for the Romberg sign, which is characterized by the presence of impaired balance while a person stands on a narrow base with closed eyes, a finding that this patient was noted to have. However, sensory ataxia is generally accompanied by impairment in proprioception or by diminished reflexes, neither of which this patient had. Similarly, no clinical findings of vestibular disease were elicited. Therefore, I think that this patient's ataxia originated from a disease of the cerebellum itself. I would ask whether this patient had impaired balance while standing on a narrow base with her eyes open, a finding that would be consistent with disease of the cerebellum.

Another important function of the cerebellum is oculovestibular coordination. This patient had saccadic dysmetria and impaired smooth pursuit, which localize to the dorsal vermis and the flocculonodular lobe of the cerebellum.[1] Square-wave jerks, which were noted in this patient, are typically asymptomatic and are distinct from other eye-movement disorders, such as nystagmus, opsoclonus, and ocular flutter. Square-wave jerks can occur in patients with disorders of the cerebellar and extracerebellar central nervous system.

The cerebellum also has cognitive and affective function, which localizes to the posterior lobe. Deficits resulting from damage to the cognitive cerebellum have been characterized as the cerebellar cognitive affective syndrome,[2] which can be considered a "dysmetria of thought."[3] This syndrome is characterized by deficits in executive function, linguistic fluency, and visuospatial performance, as well as by neuropsychiatric symptoms. However, focal cortical cognitive deficits should be considered red flags indicative of extracerebellar disease.[4] A true amnestic deficit, which was seen in this patient, is not part of the cerebellar cognitive affective syndrome. In

fact, most patients with disease that is limited to the cerebellum have scores in the normal range on bedside cognitive screening tests such as the Montreal Cognitive Assessment,[4] whereas this patient had a score that indicated dementia. In addition, cerebellar disease does not lead to spontaneous abnormal movements. This patient began to have uncontrollable arm jerks that were consistent with myoclonus — another sign that extracerebellar structures were becoming involved as her disease progressed. Lastly, the EEG showed a single spike, indicating cortical irritability, which also points to extracerebellar involvement.

The differential diagnosis in this patient is focused on a subacute progressive disease that starts in the cerebellum and spreads to other parts of the central nervous system. This "ataxia plus" syndrome could be the result of a toxic or metabolic disorder, infection, leptomeningeal carcinomatosis, an immune-mediated condition, or neurodegeneration.

#### TOXIC AND METABOLIC DISORDERS

Substances of abuse, such as alcohol, can cause ataxia, as can a number of medications, including antiepileptic agents and sedatives.[5,6] However, the patient was not taking any of these drugs, and her history of alcohol use was modest. I would ask specifically about the use of bismuth subsalicylate, a widely available over-the-counter medication for gastrointestinal ailments. Overuse of bismuth can cause subacute changes in mental state and amnesia — symptoms that are sometimes misdiagnosed as Alzheimer's disease or Creutzfeldt–Jakob disease. Myoclonus and ataxia can be prominent, and EEG may reveal epileptiform abnormalities. However, given that the patient had no known history of exposure to bismuth, I will consider alternative diagnoses.

Environmental exposure to heavy metals, particularly mercury, can cause an ataxic syndrome.[7] The toxic effects of manganese can also include movement disorders.[5] Although no manganese level was reported for this patient, she was appropriately screened for exposure to other heavy metals, and all such screening tests were negative.

Wernicke's encephalopathy can cause acute ataxia, ophthalmoplegia, and confusion in patients who are nutritionally deficient in thiamine. Despite this patient's normal results on MRI of the head, Wernicke's encephalopathy cannot be ruled out on the basis of these findings, given that MRI findings are specific, but not sensitive, for this disease.[8] However, this patient did not have a history of alcohol use disorder, bariatric surgery, or prolonged vomiting — characteristics that would have suggested an increased risk for a nutritional deficiency. Therefore, a diagnosis of Wernicke's encephalopathy is unlikely.

#### INFECTION

Cerebellitis can occur as either a direct infection or a parainfectious phenomenon.[9,10] Both variants are more common in children than in adults. Varicella–zoster infection is the most common cause of cerebellitis in adults, but I would expect a more acute presentation and evidence of inflammation in the CSF. Listeria rhombencephalitis can be acute or subacute, and it occurs primarily in older adults, especially among those who are immunosuppressed.[11] Neurologic Whipple's disease is characterized by subacute dementia, ataxia, and myoclonus.[12,13] In both listeria rhombencephalitis and neurologic Whipple's disease, MRI of the head may occasionally be normal, but the absence of evidence of inflammation in this patient's CSF makes these diagnoses unlikely.

JC virus has a predilection for white matter of the cerebellum and its peduncles.[14,15] However, JC virus infection is a disease that occurs in immunosuppressed patients and causes characteristic brain lesions that can be seen on MRI; therefore, JC virus infection is an unlikely diagnosis in this case.

#### LEPTOMENINGEAL CARCINOMATOSIS

Patients with leptomeningeal carcinomatosis can have a subacute syndrome that includes ataxia. MRI may or may not show signal hyperintensity in the cerebellar sulci on T2-weighted FLAIR images or enhancement in the cerebellar sulci on gadolinium-enhanced images.[16] Given that this patient had a normal CSF protein level and cell count, leptomeningeal carcinomatosis is very unlikely.[17]

#### IMMUNE-MEDIATED CONDITIONS

Paraneoplastic cerebellar degeneration is defined as ataxia that develops within 5 years before or after a diagnosis of cancer, and ataxia predates the cancer diagnosis in 65% of cases. This pa-

tient's tests for paraneoplastic antibodies in the blood and CSF were negative, but 18% of affected patients are seronegative. However, PET-CT from the skull base to the thighs was unremarkable in this patient. Therefore, a diagnosis of paraneoplastic cerebellar degeneration is unlikely.

Autoimmune cerebellar ataxia is a syndrome that is similar to paraneoplastic cerebellar degeneration, but affected patients have no evidence of cancer.[18] A disease characterized by an association of cerebellar ataxia with antibodies related to celiac disease has been described, but the disease course is typically slower than that seen in this patient. A cerebellar variant of Hashimoto's encephalopathy that is associated with antibodies to thyroid peroxidase and thyroglobulin, which were seen in this patient, has been described. However, approximately 15% of the population has seropositivity for thyroid peroxidase and thyroglobulin antibodies, making attribution of neurologic symptoms to the presence of these antibodies tenuous at best. In addition, the disease course is usually slower than that seen in this patient, and the CSF findings are typically abnormal. Therefore, Hashimoto's encephalopathy is unlikely. Nevertheless, immunosuppressive therapy was administered when the diagnosis of autoimmune cerebellitis was considered.[19] The patient's neurologic disease progressed despite this treatment.

### NEURODEGENERATION

Sporadic Creutzfeldt–Jakob disease is the most common human prion disease and has a broad and heterogeneous spectrum of manifestations. The cerebellar form of Creutzfeldt–Jakob disease (Brownell–Oppenheimer variant) is characterized by a cerebellar syndrome with no evidence of cognitive impairment in the first month of illness, and it accounts for approximately 20% of cases of sporadic Creutzfeldt–Jakob disease.[20,21] The mean age at onset is 63 years, and the first symptoms that occur are most commonly gait dysfunction, dizziness, and incoordination, all of which are consistent with this patient's presentation. Cognitive impairment occurs a mean of 3 months after the onset of ataxic symptoms — a clinical course that closely matches this patient's course. Other neurologic features, such as pyramidal signs, myoclonus, or vision impairment, become evident with progression; these findings were also observed in this patient.

Does the absence of abnormal findings on MRI or EEG make Creutzfeldt–Jakob disease unlikely? Abnormal MRI findings usually occur at some point in the disease course, but they may initially be subtle or misread.[22,23] EEG has low sensitivity for the cerebellar form of Creutzfeldt–Jakob disease. I think this patient's presentation is most consistent with the cerebellar form of Creutzfeldt–Jakob disease. To establish this diagnosis, I would obtain CSF to perform tests for markers of neuronal damage, such as 14-3-3 protein and total tau, as well as a real-time quaking-induced conversion (RT-QuIC) assay.

*Dr. Meridale V. Baggett* (Medicine): Dr. Schmahmann, what was your clinical impression when you evaluated this patient?

*Dr. Jeremy D. Schmahmann:* This patient had cerebellar ataxia that had developed over a period of days to a few weeks, with a limited differential diagnosis of potentially life-threatening conditions. On presentation to this hospital, the patient's care was managed with the same degree of urgency as would be the care of a patient with acute change in mental status, with a focus on identifying reversible conditions. She was treated with high-dose thiamine but had no response. Creutzfeldt–Jakob disease was considered during her initial admission to this hospital, since the classic EEG and MRI findings can be delayed in onset. However, because immune-mediated ataxias can mimic Creutzfeldt–Jakob disease, the patient received immunosuppressive therapy, despite a negative evaluation for cancer and paraneoplastic antibodies. We took the approach of treating the potentially curable conditions while waiting for the results of the Creutzfeldt–Jakob disease tests.

The patient had no response to immunosuppressive therapy. As the disease progressed, her cognitive issues evolved into an amnestic dementia, making Creutzfeldt–Jakob disease the most likely diagnosis from a clinical perspective.

### CLINICAL DIAGNOSIS

Probable Creutzfeldt–Jakob disease.

### DR. BART K. CHWALISZ'S DIAGNOSIS

Cerebellar form of Creutzfeldt–Jakob disease.

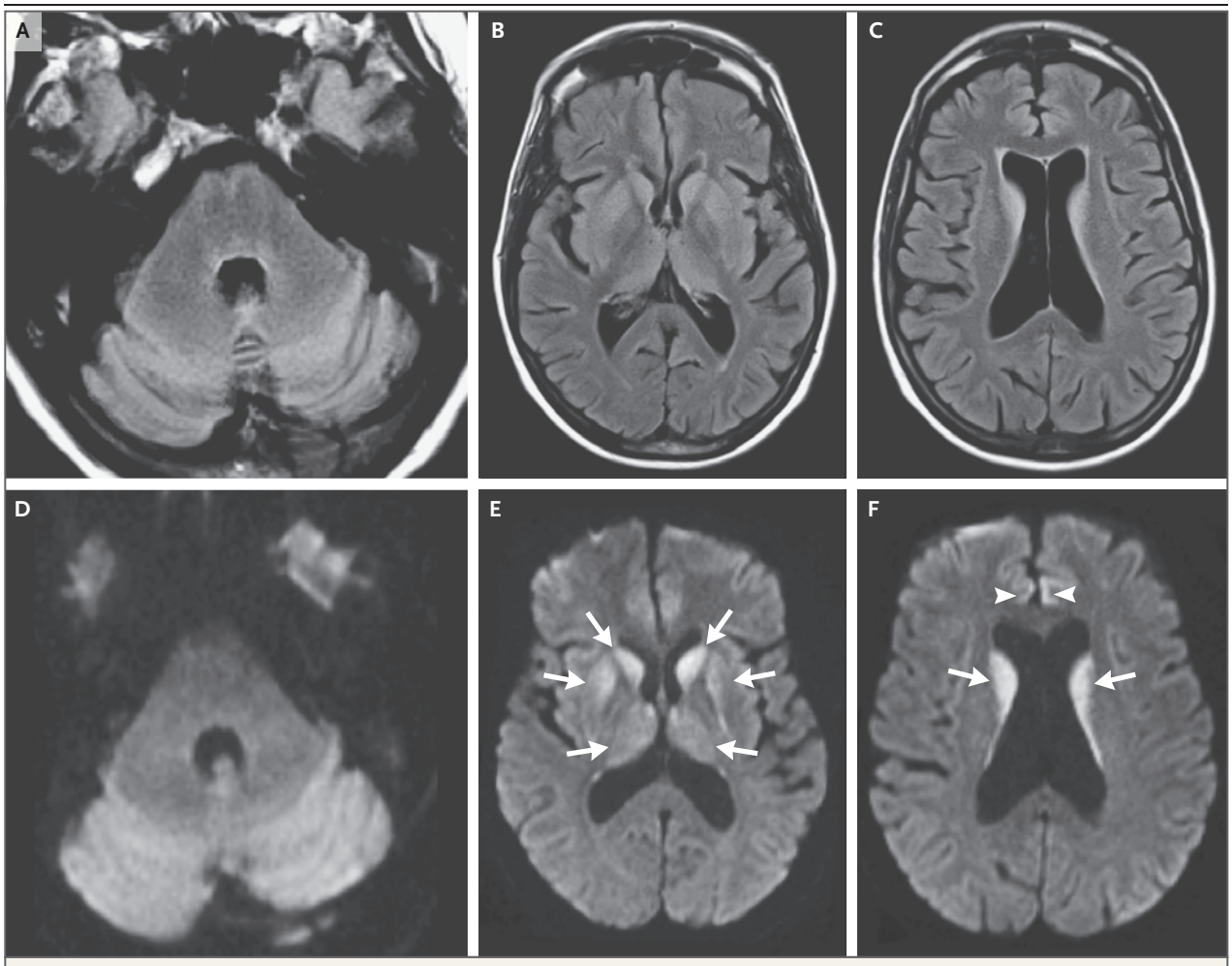


**Figure 2. MRI of the Head Obtained at the Time of the Second Admission.**

Axial T2-weighted FLAIR images (Panels A, B, and C) show mild signal hyperintensity in the bilateral basal ganglia and thalami. Diffusion-weighted images (Panels D, E, and F) show pronounced signal hyperintensity in these locations that is most conspicuous in the caudate nuclei (Panels E and F, arrows). Diffusion-weighted images also show subtle hyperintensity in the anterior cingulate gyri (Panel F, arrowheads) that is more prominent on the left than the right, but the cerebral cortex is otherwise spared. No definite abnormality is identified in the cerebellum.

## DIAGNOSTIC STUDIES

*Dr. Buchbinder:* MRI of the head was performed before and after the administration of intravenous contrast material at the time of the patient's second admission to this hospital (3 weeks after discharge from the first admission to this hospital). T2-weighted FLAIR imaging showed mild signal hyperintensity in the bilateral basal ganglia and thalami that was most conspicuous in the caudate nuclei. Diffusion-weighted imaging showed pronounced signal hyperintensity in these locations, as well as subtle hyperintensity in the anterior cingulate gyri that was more prominent on the left than the right, but the cerebral cortex appeared otherwise normal. No definite signal abnormalities were identified in the cerebellum (Fig. 2). Retrospectively, MRI of the head that was performed at the time of the patient's first admission to this hospital showed subtle signal hyperintensity in the striatum and thalami on T2-weighted FLAIR images as well as on diffusion-weighted images. Although hypoxic–ischemic, metabolic, infectious, and autoimmune

processes may manifest with similar findings on neuroimaging, in the context of this patient's clinical presentation, the imaging is characteristic of sporadic Creutzfeldt–Jakob disease.[24]

The findings on MRI of the head in this patient were also consistent with the cerebellar form of Creutzfeldt–Jakob disease; in this variant, diffusion-weighted imaging and T2-weighted FLAIR imaging frequently show signal hyperintensity in the basal ganglia and thalami, with relative sparing of the cerebral cortex.[25,26] Even in patients who have pronounced cerebellar ataxia and proven pathological features of the cerebellar form of Creutzfeldt–Jakob disease, signal hyperintensity on diffusion-weighted imaging and T2-weighted FLAIR imaging is usually absent in the cerebellum.[26-28]

*Dr. Wesley R. Samore:* The pathogenesis of Creutzfeldt–Jakob disease centers around cellular prion protein ($PrP^{C}$), a cell-surface glycoprotein of unknown function that is abnormally folded into the scrapie form ($PrP^{Sc}$). $PrP^{Sc}$ replicates itself by misfolding $PrP^{C}$ into $PrP^{Sc}$ by means of post-translational modification.[29] Creutzfeldt–Jakob disease may be classified as sporadic, familial, or acquired, with the sporadic form accounting for approximately 85 to 90% of cases.[30]

In this patient, the level of total tau in the CSF was greater than 4000 pg per milliliter (reference range, 0 to 1149), and the CSF 14-3-3 protein assay was positive. Both tau and 14-3-3 are released into the CSF during the development of rapid neuronal damage, but their presence in the CSF is not specific to neuronal damage induced by $PrP^{Sc}$. Both tests can detect Creutzfeldt–Jakob disease with a sensitivity of greater than 90%; however, specificity is near 80%.[31,32]

The CSF RT-QuIC assay has emerged as the reference-standard test for the diagnosis of Creutzfeldt–Jakob disease, and this patient's assay was positive. The RT-QuIC assay directly tests the inherent infectivity of $PrP^{Sc}$ by reproducing the misfolding process in vitro.[33] With the use of recombinant, conformationally normal prion protein as a substrate, $PrP^{Sc}$ that is present in the sample of CSF replicates itself during cycles of vigorous shaking. The accumulated misfolded prion protein is detected with the use of thioflavin T. The RT-QuIC assay detects Creutzfeldt–Jakob disease with a sensitivity of 92% and a specificity of 99 to 100%.[34]

*Dr. Schmahmann:* Once the diagnosis was definitively made, both the patient and her family were understandably distraught. Nevertheless, they showed insight, resilience, and fortitude that was remarkable and inspiring, coming together to face the challenges of the next few months.

During the second hospitalization, the patient's condition declined clinically each day. Language became progressively impaired, with phonemic paraphasias, confusion, and conflation of events and perseveration. A mild degree of fear and paranoia became evident in the background of her otherwise pleasant and affable demeanor. The ataxia and dysarthria became progressively disabling.

The patient was discharged home with hospice care after multiple in-depth conversations with the family. She died surrounded by her family 4 months after the onset of the disease.

The importance of autopsy had been discussed with the patient and her husband before death because of the need to understand this catastrophic illness in greater detail. At the time of death, the family granted permission for an autopsy of the brain only.

## AUTOPSY FINDINGS

*Dr. Samore:* Gross examination of the brain was unremarkable. On histologic examination, marked spongiform degeneration — the morphologic hallmark of Creutzfeldt–Jakob disease — was present in the basal ganglia (Fig. 3A), thalamus, and cerebellum (Fig. 3B). These regions had concomitant gliosis and neuronal dropout. In addition, the molecular cell layer of the cerebellum was markedly atrophic. Kuru plaques were not identified. There was evidence of focal, marked spongiform degeneration in the cingulate cortex (Fig. 3C); however, the remaining cerebral cortex was largely unremarkable (Fig. 3D).

After the histologic examination was performed, the brain was sent to the National Prion Disease Pathology Surveillance Center for analysis. Immunohistochemical staining for 3F4, the monoclonal antibody to prion protein, revealed granular deposits in the brain. In the context of the autopsy findings, the findings on immunohistochemical analysis verified the diagnosis of Creutzfeldt–Jakob disease. The distribution of the patient's disease on the basis of histopathologi-

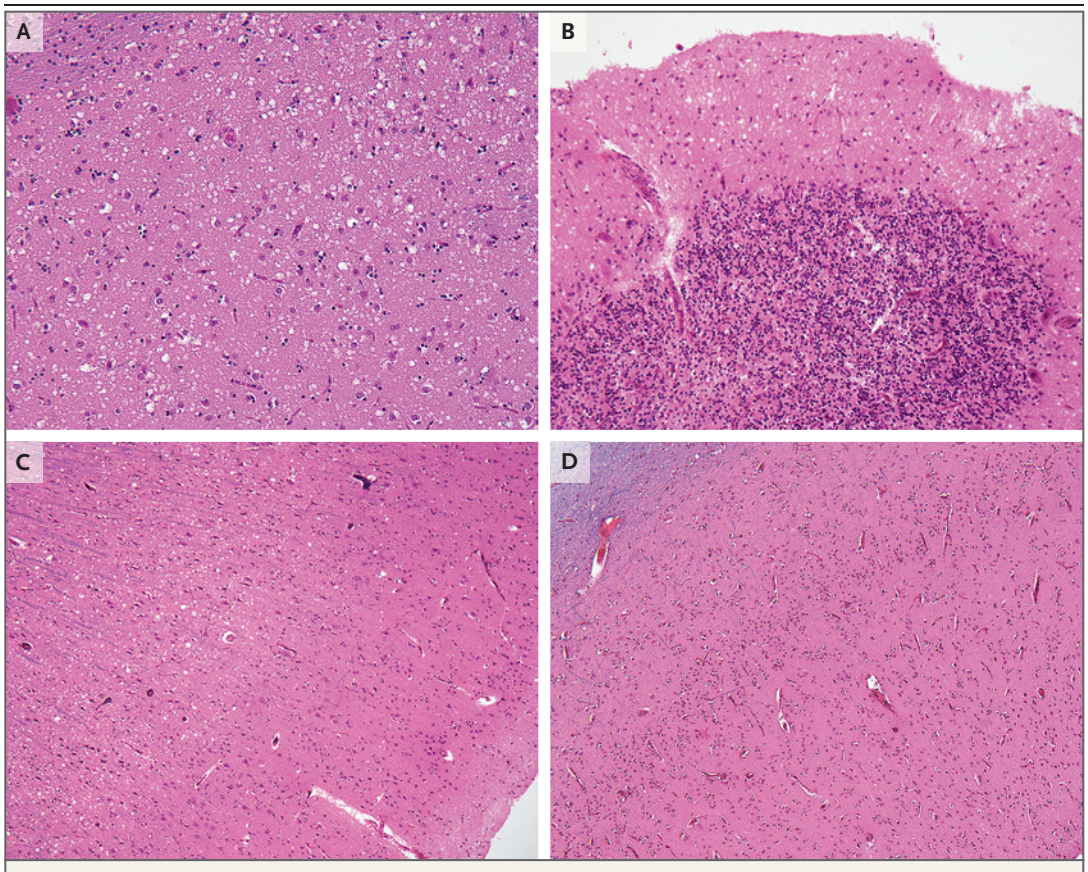


**Figure 3. Microscopic Specimens of the Brain Obtained at Autopsy.**

Luxol fast blue–hematoxylin and eosin staining of the autopsy specimens was performed. Shown in the putamen (Panel A) is marked spongiform degeneration, as evidenced by the numerous clear vacuoles within the neuropil. In the cerebellum (Panel B), spongiform degeneration with atrophy of the molecular cell layer can be seen (upper portion of the image). Focally in the cingulate gyrus (Panel C), spongiform degeneration is present in the deep cortical layers (upper left), with the superficial layers spared (lower right). The frontal cortex (Panel D) is unremarkable, with a full neuronal complement and no spongiform degeneration.

cal examination fit most closely with the cerebellar form of Creutzfeldt–Jakob disease, as evidenced by marked spongiform degeneration in the basal ganglia, thalamus, and cerebellum, with the neocortex less affected.

*Dr. Schmahmann:* After the autopsy was performed, we had a full debriefing with the family about the findings. They appreciated receiving the definitive results, had questions about the disease origin and implications for the family, and were extremely supportive of allowing the information derived from the patient's case to be used for the purposes of education and research.

As the knowledge of Creutzfeldt–Jakob disease increases, particularly with respect to its manifestations and underlying neurobiologic features, the hope is that Creutzfeldt–Jakob disease will transition from being a fatal disease to one that we can rapidly identify, treat, and cure.

## ANATOMICAL DIAGNOSIS

Creutzfeldt–Jakob disease.

This case was presented at Neurology Grand Rounds.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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