

A Prion Disease—Possible Gerstmann-Straussler-Scheinker Disease

A Case Report

Ayşe Aralasmak, MD, Barbara J. Crain, MD, PhD,† Wen-Quan Zou, MD, PhD,‡ and David M. Yousem, MD, MBA**

Summary: A 50-year-old patient with a 6-month history of progressive cognitive and motor disability is presented. There were no myoclonic jerks on examination and no periodic sharp waves by electroencephalography. Imaging showed high signal on T2-weighted scans in the basal ganglia and posterior limbs of the internal capsules, with no restricted diffusion and parenchymal volume loss. A brain biopsy was performed. Western blot analysis revealed a protease-resistant prion protein fragment (PrP⁷⁻⁸), the molecular hallmark of Gerstmann-Straussler-Scheinker disease.

Key Words: prion diseases, Gerstmann-Straussler-Scheinker, magnetic resonance imaging findings

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Prion diseases are inevitably fatal neurodegenerative conditions that affect people and a wide variety of animals.¹ They are the result of accumulation of a protease-resistant form of a host-derived prion protein.^{1,2} Although prion diseases may have certain morphologic and pathophysiologic similarities to other progressive dementing disorders, such as Alzheimer and Parkinson disease, they typically occur at an earlier age. Most cases of prion diseases are sporadic, but there are familial forms. In addition, prion diseases are occasionally transmitted by inoculation or ingestion of prion-contaminated material.¹ Gerstmann-Straussler-Scheinker disease (GSS) is a genetic form of the prion disease. Cognitive decline is usually associated with cerebellar disorders and postural abnormalities in this disorder.^{2–4} Most imaging studies document cerebral and cerebellar atrophy.^{3,5} We present a patient with a family history of dementia, who complained of a 6-month history of language difficulty and tremor. The only imaging finding was T2-weighted signal intensity abnormality in the basal ganglia

and posterior limbs of the internal capsules without definite parenchymal volume loss and restricted diffusion. Genetic testing was not available. Western blot studies of brain biopsy tissue confirmed the diagnosis of prion disease, possibly GSS.

CASE REPORT

A 50-year-old man presented with 6 months of progressive difficulty in word finding and language output, fine tremors, dysphagia, dysarthria, hoarseness, memory loss, gait difficulties, disorder in movement of his upper extremities, incontinence, decreased appetite, and weight loss.

Neurologic examination revealed increase in muscle tone, diffuse fine tremor, hyperreflexia, and unsteady gait. Primitive reflexes, such as palmomental and glabellar reflexes, were present and suggested higher cortical dysfunction. There was no evidence of dysesthesia to suggest posterior neuron involvement or spinocerebellar degeneration. Cerebellar tests were difficult to assess because of the tremor. The differential diagnosis included various dementing disorders. The patient underwent extensive assessment, including neurophysiologic tests and multiple cerebrospinal fluid analyses. The result of a cerebrospinal fluid 14-3-3 protein assay done at the National Prion Disease Pathology Surveillance Center was negative. Electroencephalography showed no specific abnormalities. In particular, there were no seizures or periodic sharp waves. Electromyography and nerve conduction studies were limited due to the presence of tremors; however, the findings demonstrated normal motor unit potentials with no evidence of fibrillation or fasciculation.

On imaging evaluation (Figs. 1, 2), there were symmetric, nonenhancing, increased signal intensity changes on the T2-weighted and diffusion-weighted images. The abnormalities involved the basal ganglia and posterior limbs of the internal capsules. There were no corresponding signal changes on the apparent diffusion coefficient maps. The cerebellum was unremarkable. No definite parenchymal volume loss was appreciated.

Evaluations for amyotrophic lateral sclerosis, Hashimoto encephalopathy, Whipple disease, and a paraneoplastic syndrome were negative. There was no exposure to Lyme disease, ticks, rabies, neurotoxins, or biologic agents. The patient had worked in a navy shipyard as a nuclear pipe fitter for 20 years and may have been exposed to radiation and some chemicals. Serologic testing was negative for mumps and lymphocytic choriomeningitis as well as for Western equine, herpes simplex, West Nile, La Crosse, and California encephalitis. There was a maternal history of dementia.

Right frontal dural and neocortical biopsies were performed. Because of the short clinical history, the specimen was treated as a possible prion disease case. The dura and a portion of the neocortex were processed for histologic examination according to standard techniques, including formic acid pretreatment for prion disease.

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From the *Russell H. Morgan Department of Radiology and Radiological Science, Division of Neuroradiology, Johns Hopkins Medical Institutions, Baltimore, MD; †Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, MD; and ‡Institute of Pathology, Neuropathology Division, Case Western Reserve University, Cleveland, OH.

Reprints: Ayşe Aralasmak, 600 North Wolfe Street, Phipps B-112, Baltimore, MD, 21287 (e-mail: aysearalasmak@hotmail.com).

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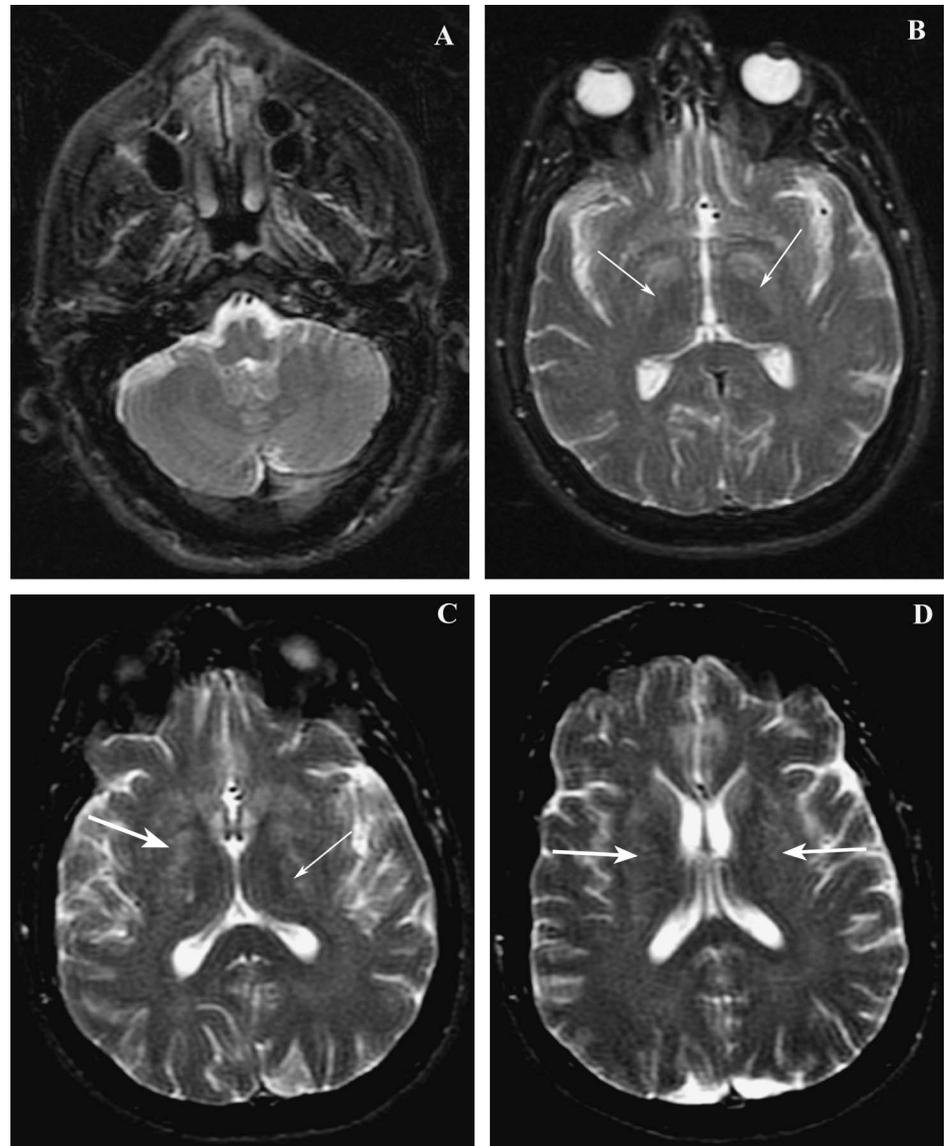


FIGURE 1. Magnetic resonance imaging study. Extra-axial spaces are within the normal range for age. A, There is no definite cerebellar atrophy. C, D, Symmetric high T2-weighted signal changes are seen in basal ganglia (arrows). B, C, Signal changes involve the posterior limbs of the internal capsules (thin arrows).

Microscopic examination showed that the dura was unremarkable. The neocortex showed mild astrogliosis that was best seen in the underlying white matter (Fig. 3).

Immunohistochemistry was negative for ubiquitin, phosphorylated- τ , β -amyloid, and α -synuclein. The paraffin blocks and a fresh-frozen portion of neocortex were therefore referred to the National Prion Disease Pathology Surveillance Center. Prion protein (PrP) immunohistochemistry was carried out on paraffin sections according to previous procedures⁶ and showed possible weak immunostaining of PrP at most. Western blot analysis was performed on the frozen sample according to previously published methods.⁷ This analysis demonstrated a clearly detectable PrP band migrating at 7-8 kd after treatment with proteinase K (PrP7-8). The diagnosis of prion disease, possibly GSS, was made. The lack of definite spongiform change and immunohistochemically demonstrable prion protein may reflect a sampling error, the relatively early stage of the disease, or the particular genetic alteration in this patient, because there is considerable heterogeneity in the histologic presentation of GSS.^{3,4,8}

During the months since surgery, the patient has become more confused and obtunded, weakness has increased in his legs, and his gait has become shuffled.

DISCUSSION

Prion diseases are characterized by misfolding of the normal host cellular prion protein (PrP^C) into an abnormal form called prion protein scrapie (PrP^{Sc}).^{1,2} The function of PrP^C is not known, but it may have roles in antioxidant systems and cellular copper metabolism.² The PrP^{Sc} is relatively insoluble and relatively protease resistant and accumulates as amyloid in tissues of the central nervous system.² The deposition of PrP^{Sc} eventually results in neuropathologic changes of neuronal loss, astrocytic gliosis, and spongiform changes,

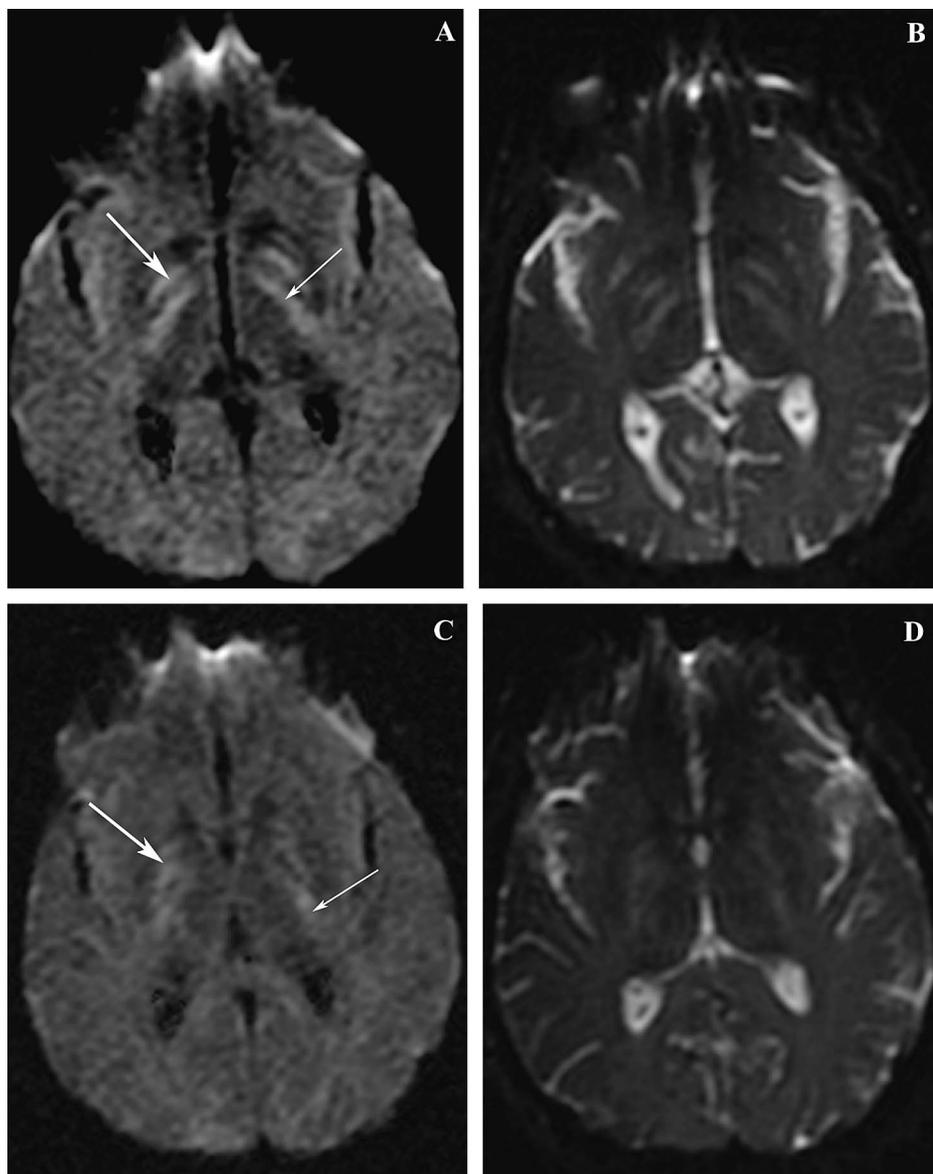


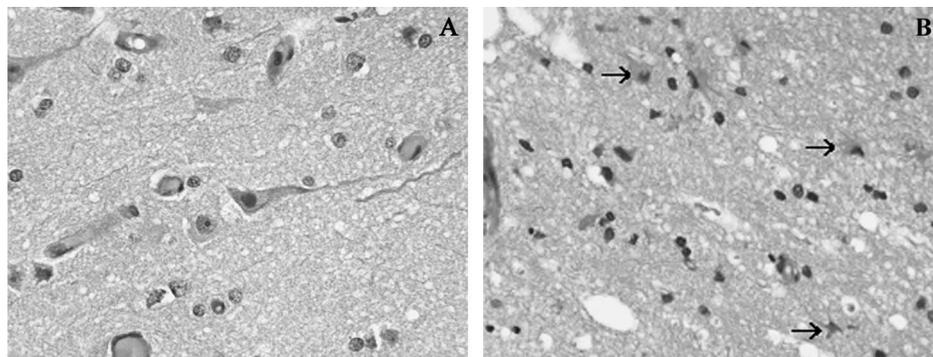
FIGURE 2. Diffusion-weighted images (A, C) and corresponding apparent diffusion coefficient maps (B, D). A T2 shine-through effect is seen in the inferior aspect of the basal ganglia (arrows) and posterior limbs of the internal capsules (thin arrows). The brightness on diffusion-weighted images is more extensive than that normally seen secondary to minimal restrictive diffusivity along the descending tracts.

which are the typical hallmarks of the prion diseases.^{1,2} Prion diseases occur in a wide range of animals and can be transmitted within and sometimes between animal species.^{1,2} Different types of human prion diseases are described in Table 1.

In general, definitive diagnosis of a prion disease requires brain biopsy or autopsy with immunohistologic and genetic studies,^{1,2} although a tonsil biopsy may be sufficient in variant Creutzfeldt-Jakob disease (CJD).² There are also ancillary tests that can be useful. Electroencephalography usually demonstrates periodic sharp waves (PSW) in sporadic CJD but not in variant CJD and GSS.² Cerebrospinal fluid testing for the 14-3-3 protein in the cerebrospinal fluid can also be helpful.^{1,2} Elevated levels of this protein have also been reported in nonprion diseases such as encephalitis, cerebral infarction, and paraneoplastic neurologic disorders.¹

Magnetic resonance imaging can be helpful for diagnosing specific types of human prion diseases. The pulvinar sign, a high T2-weighted signal change in the posterior thalamus,^{1,2,9} as well as signal change in the dorsomedial nucleus of the thalamus² seems to be relatively unique for variant CJD and is present in approximately 75% of the cases.¹ In contrast, symmetric signal changes in the basal ganglia and cerebral cortex with diffusion restriction have high sensitivity and specificity to sporadic CJD.^{1,2,9} Diffusion-weighted images may be even more sensitive than T2-weighted scans for sporadic CJD-like diseases. In fatal familial insomnia, the magnetic resonance imaging scan is usually normal, although it may show nonspecific cerebral or cerebellar atrophy. Positron emission tomography demonstrates characteristic reduced activity in the thalami in this disorder.^{3,10}

FIGURE 3. Histologic results. A, Gray matter is unremarkable in sections stained with hematoxylin–eosin. B, Underlying white matter shows reactive astrocytes (arrows). The sponginess in the background reflects exposure of the edges of the specimen to saline rather than true spongiform change.



In its classic forms, GSS is characterized clinically by progressive ataxia, parkinsonian symptoms, and dementia and biochemically by the presence of protease-resistant PrP⁷⁻⁸ in the central nervous system.²⁻⁴ Histopathologically, degeneration has been shown in the ascending and descending columns and cerebellar dentate nuclei.^{3,4} The usual imaging findings for GSS are volume loss in the cerebellum or diffuse volume loss in the cerebrum and cerebellum^{3,5} and,

rarely, decreased T2-weighted signal changes in the basal ganglia.¹¹ The present case is the first report of high signal changes on T2-weighted scans in the basal ganglia and posterior limbs of the internal capsules encompassing the corticopyramidal and parts of the corticobulbar tracts. Damage to these structures could explain the patient's extrapyramidal, pyramidal, and corticobulbar degenerative symptoms.

TABLE 1. Clinical, Diagnostic, and Imaging Findings of Human Prion Diseases

Prion Diseases	Sporadic		Acquired		Genetic	
	Sporadic CJD	Iatrogenic CJD	Variant CJD	Familial CJD	GSS	FFI
Transmission	Unknown cause, evenly distributed in the world ²	Contamination by prion-infected dura and cornea implants or human cadaveric pituitary extracts ^{1,2}	Transmission of bovine prion disease to people by contaminated meat products ^{1,2}	Family history may or may not be present; many mutations to prion nucleoprotein at chromosome 20; autosomal dominant inheritance with high penetrance; variable phenotypes, overlapping symptoms can be found ²		
Age and duration of illness	55–65 years; 4–5 months' duration ^{1,2}	Depends on age and site of inoculation (mean duration of 16 months but up to 30 years) ^{1,2}	Median age of 29 years; 14 months' duration ²	Earlier age of onset and longer duration than sCJD ^{1,2}	40–60 years; ⁶ 5 years' duration ^{2,3,8}	50 years; 13–15 months' duration ^{2,3}
Clinical symptoms and EEG findings	Cognitive impairment followed by extrapyramidal and pyramidal findings, MJ ⁺ , PSW ⁺ ^{1,2}	Similar to sCJD ¹	Psychiatric symptoms followed by cognitive decline and ataxia, MJ ⁻ , PSW ⁻	Similar to sCJD ^{1,2}	Cerebellar signs, ataxia, postural abnormalities, and cognitive decline, MJ ⁻ , PSW ^{-1,2,5}	Sleep and autonomic disturbances such as sympathetic hyperactivity ^{2,3}
MRI findings	Symmetric signal change in basal ganglia and cortices; associated restricted diffusion ^{1,2,9}	Limited data but signal changes in the basal ganglia ²	Symmetric signal abnormality in posterior thalamus (pulvinar sign) and dorsomedial nucleus of thalamus with no restricted diffusion ^{1,2,9}	Similar to sCJD ^{1,2}	Cerebral and cerebellar atrophy, basal ganglia abnormality, no restricted diffusion ^{3,5,10}	Normal or nonspecific cerebral and cerebellar volume loss, reduced activity in thalami on PET ^{1,3,11}
Neuropathology	Spongiform changes, neuronal loss, astrocytosis, and variable pattern of prion protein plaques ²	Similar to sCJD ¹	Spongiform changes, neuronal loss, astrocytosis, and florid prion protein plaques ²	Similar to sCJD ^{1,2}	Neuronal loss, astrocytosis, multicentric and other prion protein plaques, variable spongiform changes ^{3,4,8}	Thalamic involvement, typically without spongiform changes ³

EEG, electroencephalography; FFI, Familial fatal insomnia; MJ, myoclonic jerks; MRI, magnetic resonance imaging; PET, positron emission tomography; PSW, periodic sharp waves; sCJD, sporadic Creutzfeldt-Jakob disease; +, positive; -, negative.

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