Movement Disorders
CLINICAL PRACTICE

RESEARCH ARTICLE

Gerstmann-Sträussler-Scheinker Disease Presenting as Late-Onset Slowly Progressive Spinocerebellar Ataxia, and Comparative Case Series with Neuropathology

Christopher D. Stephen, MB, ChB, FRCP, SM,[1,2,3,*] Claudio Melo de Gusmao, MD,[4,5] Sharan R. Srinivasan, MD, PhD,[6] Abby Olsen, MD, PhD,[7] Fernando Freua, MD,[4] Fernando Kok, MD,[4] Renata Montes Garcia Barbosa, MD,[4] Jin Yun (Helen) Chen, MS, CGC,[8,9] Brian S. Appleby, MD,[10] Thomas Prior, PhD,[10] Matthew P. Frosch, MD, PhD,[9] and Jeremy D. Schmahmann, MD[1,2,3]

Abstract: Background: Genetic prion diseases, including Gerstmann-Sträussler-Scheinker disease (GSS), are extremely rare, fatal neurodegenerative disorders, often associated with progressive ataxia and cognitive/neuropsychiatric symptoms. GSS typically presents as a rapidly progressive cerebellar ataxia, associated with cognitive decline. Late-onset cases are rare.

Objective: To compare a novel GSS phenotype with six other cases and present pathological findings from a single case.

Methods: Case series of seven GSS patients, one proceeding to autopsy.

Results: Case 1 developed slowly progressive gait difficulties at age 71, mimicking a spinocerebellar ataxia, with a family history of balance problems in old age. Genome sequencing revealed a heterozygous c.392G > A (p.G131E) pathogenic variant and a c.395A > G resulting in p.129 M/V polymorphism in the *PRNP* gene. Probability analyses considering family history, phenotype, and a similar previously reported point mutation (p.G131V) suggest p.G131E as a new pathogenic variant. Clinical features and imaging of this case are compared with those six additional cases harboring p.P102L mutations. Autopsy findings of a case are described and were consistent with the prion pathology of GSS.

Conclusions: We describe a patient with GSS with a novel p.G131E mutation in the *PRNP* gene, presenting with a late-onset, slowly progressive phenotype, mimicking a spinocerebellar ataxia, and six additional cases with the typical P102L mutation.

Gerstmann-Sträussler-Scheinker disease (GSS) is a rare, autosomal dominant adult-onset hereditary movement disorder caused by pathogenic variants in the *PRNP* gene. Affected individuals typically have a positive family history, with symptom onset in the 5th decade, manifesting with ataxia and slowly progressive dementia. However, significant phenotypic variability exists, and

[1]*Ataxia Center, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA;* [2]*Cognitive Behavioral Neurology Unit, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA;* [3]*Laboratory for Neuroanatomy and Cerebellar Neurobiology, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA;* [4]*Movement Disorders Division, Department of Neurology, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts, USA;* [5]*Department of Neurology, University of São Paulo, São Paulo, Brazil;* [6]*Movement Disorders Division, Department of Neurology, University of Michigan, Ann Arbor, Michigan, USA;* [7]*Movement Disorders Division, Department of Neurology, University of Pittsburgh and UPMC, Pittsburgh, Pennsylvania, USA;* [8]*Neurogenetics Unit, Department of Neurology, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA;* [9]*C.S. Kubik Laboratory of Neuropathology, Department of Pathology, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts, USA;* [10]*The National Prion Disease Pathology Surveillance Center, Case Western Reserve University, Cleveland, Ohio, USA*

***Correspondence to:** Dr Christopher D. Stephen, Department of Neurology, Massachusetts General Hospital, 100 Cambridge Street, Suite 2000, Boston, MA 02114, USA; E-mail: cstephen@mgh.harvard.edu
Keywords: Gerstmann-Sträussler-Scheinker disease, prion disease, ataxia, spinocerebellar ataxia.
Received 7 June 2023; revised 11 December 2023; accepted 3 January 2024.
Published online 00 Month 2024 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13976

up to 16.5% of cases may not have a family history.[1–3] Prevalence is 1–100/100,000,000.[4] Pathophysiology reveals multifocal prion protein plaques in the cerebellum and cerebral cortex. The *PRNP* p.P102L variant is commonly encountered, however, several other variants (including point mutations and repeat insertions) have been reported.[1] Neuroimaging can be normal, or demonstrate cerebellar, brainstem, or cerebral hemispheric atrophy, white matter lesions, and T2/diffusion-weighted hyperintensities in the cortex or caudate/putamen.[1,2,4,5] The presence of basal ganglia hyperintensities are associated with more rapid progression and shorter disease duration.[4] Cerebrospinal fluid (CSF) may reveal elevated 14-3-3, total tau, or β-amyloid levels,[6] and while real-time quaking-induced conversion (RT-QuIC) test has a high sensitivity for sporadic Creutzfeld-Jacob disease (CJD), only two-thirds of GSS patients have a positive result.[7] Electroencephalography (EEG) can be normal, reveal triphasic waves, or frank epileptiform discharges.[2,4]

Tesar et al proposed four distinct phenotypes[4]: (1) typical GSS, involving early-onset ataxia, lower extremity sensory involvement, and late cognitive decline; (2) GSS with areflexia and paresthesia, with prominent early neuromuscular features, including weakness and peripheral neuropathy and later development of ataxia and dementia; (3) CJD-like GSS, with early-onset dementia and ataxia and very rapid progression; and (4) Pure dementia GSS, with early-onset, predominant dementia, late-onset ataxia and slower disease progression. Rare cases include presentation with lower extremity spasticity, parkinsonism, progressive supranuclear palsy (PSP) mimics, and optic atrophy.[4] We present a case series of seven GSS patients, encompassing the range of different phenotypes, and expand on these with a patient harboring a novel *PRNP* variant, presenting as a novel late-onset, slowly progressive pure cerebellar ataxia phenotype. We provide illustrative autopsy findings in a single case of the neuromuscular phenotype.

Case Series

Approval was obtained from the MassGeneral Brigham and University of São Paulo, Brazil research ethics committees. Records from the Massachusetts General Hospital Ataxia Center/Brigham and Women's Hospital, Boston from 1990 to 2022 were reviewed, yielding five cases, and two additional cases were identified from São Paulo, Brazil. Patients were assessed with the Brief Ataxia Rating Scale (BARS).[8] Consent was obtained for living patients.

Table 1 shows a summary of the clinical characteristics, investigations and *PRNP* genetic sequencing results of Cases 1–7. Videos 1–3 illustrate the clinical examination findings of cases 1, 6, and 7, respectively.

Case 1

This woman developed slowly progressive gait and balance problems at age 71, associated with difficulties in visual tracking. She was of Ukrainian/Romanian (maternal) and Scottish/Irish (paternal) descent. Family history (Fig. 1A) revealed several maternal family members with late-onset balance problems. Examination at age 75 (Video 1) revealed intact mentation, and mild cerebellar signs, including oculomotor abnormalities, dysarthria, lower greater than upper extremity appendicular dysmetria, mild gait ataxia (BARS 9/30), and sensory neuropathy. Montreal Cognitive Assessment (MoCA) was 30/30. Laboratory testing was normal; electromyography (EMG) showed length-dependent sensory axonal neuropathy. Vestibular testing revealed impaired fixation suppression and optokinetic nystagmus (OKN). Neuroimaging showed moderate T2 subcortical white matter lesions, without cerebellar/brainstem atrophy or diffusion-weighted abnormalities (Fig. 2A–C). Initial testing with an extended ataxia panel was negative. Whole genome sequencing revealed a novel heterozygous likely pathogenic variant c.392G > A (p.G131E) in the *PRNP* gene, subsequently confirmed by the National Prion Disease Pathology Surveillance Center (NPDPSC). This variant occurs at a highly conserved residue, is absent in GnomAD and in silico tools predict it to be deleterious. A previous substitution in the same codon (p.G131V) has been shown to alter residue flexibility contributing to prion propagation.[9] Further analysis identified the heterozygous variant c.385A > G (p.M129V), a polymorphism known to be a risk factor for prion disease.[10] Allele-specific sequencing demonstrated that both variants p.[G131E; p.M129V] occur in *cis* (ie, on the same chromosome).

Case 2

This man reported memory difficulties at age 42, although onset may have been as early as age 34, with discomfort in his lower extremities. He was of Italian descent. Family history revealed several maternal family members with ataxia and cognitive symptoms in their 30s/40s (Fig. 1B). Examination at age 44 revealed oculomotor dysmetria, dysarthria, lower extremity-predominant appendicular dysmetria and gait ataxia (BARS 11/30). Lower extremity reflexes were absent; plantar responses were mute. Over the next few years, symptoms progressed, requiring admission to a nursing home. Cognition and memory deteriorated, he developed dysphagia and sensory symptoms/paresthesias, requiring a walker. He died at age 48, bedbound and disoriented. Exome sequencing demonstrated the c.305C > T (p.P102L) variant in *PRNP*.

Case 3

This woman first noted gait difficulties at age 45. There was difficulty with handwriting and diplopia, associated with episodes of vertigo and nausea, urinary urgency, and feet numbness. She was of Chinese descent. Family history revealed ataxia and dementia in her father and brother (Fig. 1C). Examination at age 47 revealed oculomotor abnormalities, appendicular and axial ataxia, requiring a cane (BARS 13/30). There was mild sensory peripheral neuropathy and extensor plantar reflexes. By age 48, neuropathy worsened, with dysesthesias, leg weakness, and pseudobulbar affect. EMG at age 49 revealed reduced activation

TABLE 1 *Summary of GSS Cases 1–5, highlighting clinical and genetic characteristics*

Case	1	2	3	4*	5*	6	7
GSS Phenotype (per Tesar et al.)	**Late-onset SCA-like**	**Typical GSS**	**GSS with areflexia and paresthesia**	**Typical GSS**	**CJD-like GSS**	**Typical GSS**	**Typical GSS with spastic paraparesis**
Demographic details							
Sex	F	M	F	F	M	F	M
Ancestry	Eastern European/ European	European	Chinese	French Canadian/ European	French Canadian/ European	? German	Brazilian
Age at onset, years	71	42 (dysesthesia age 34)	45	54	51	37	26
Age at presentation, years	75	44	47	56	52	38	28
Age at genetic diagnosis	76	43	48	56	N/A	40	31
Duration from onset to death, years	N/A	4	6	5	4	N/A	N/A
Age at death, years	N/A	48	51	59	55	N/A	N/A
Historical features							
Family history	+	+ (dementia neuropsychiatric)	+	+*	+*	N/A	+
Initial symptoms	Gait and balance difficulties	Memory/cognitive difficulties	Gait and balance difficulties	Dysequilibrium and gait difficulties	Dysequilibrium and gait difficulties	Gait difficulties, pain, forgetfulness and labile mood	Gait difficulties, spasticity
Rate of progression	Slow	Moderate	Moderate	Rapid	Rapid	Moderate	Moderate
Cognitive dysfunction	−	+				+	+
Dementia	−	+					
Psychiatric symptoms	−					+	
Sensory symptoms	−	+ paresthesias and pain syndrome	+ numbness and burning dysesthesias			pain	−

(Continues)

TABLE 1 *Continued*

Case	1	2	3	4★	5★	6	7
GSS Phenotype (per Tesar et al.)	**Late-onset SCA-like**	**Typical GSS**	**GSS with areflexia and paresthesia**	**Typical GSS**	**CJD-like GSS**	**Typical GSS**	**Typical GSS with spastic paraparesis**
Bladder symptoms			+ Urinary urgency		+ Urinary urgency with neurogenic underactive bladder on urodynamic testing		−
Other symptoms			+ Vertigo, progressive weakness, pseudobulbar affect			+ spasticity in lower extremities	+ spastic paraparesis (unclear role of positive HTLV1 serology, CSF antibody negative)
Examination features at first visit							
Oculomotor features	Saccadic pursuit, nystagmus, hypermetric saccades	Square wave jerks, saccadic pursuit, hypermetric saccades	Saccadic pursuits, transient nystagmus, hypometric saccades	Saccadic pursuits, nystagmus, dysmetric saccades	Saccadic pursuits, transient nystagmus	Saccadic pursuits, end-gaze nystagmus, hypermetric saccades	Square wave jerks, end gaze nystagmus, saccadic pursuit
Dysarthria	+	+ (subtle)		+		+	+
UE ataxia	+	+	+	+		+	+++
LE ataxia	++	+++	++	+		+	n/a
Gait ataxia	+	+ (mild)	++	++	+ (subtle)	+++	++++
Pyramidal features			+		+/−	++	++++
Parkinsonism					+ (slight)		
LE weakness			(+++ Progressive leading to paraplegia)				++++ paraplegic
Neuropathy	+ (mild)		+				

(Continues)

TABLE 1 *Continued*

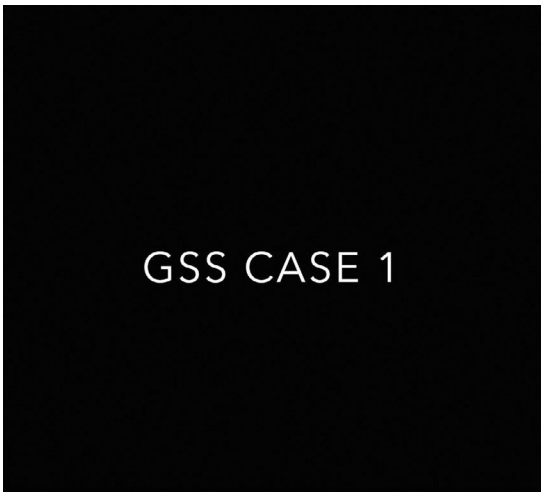
Case	1	2	3	4★	5★	6	7
GSS Phenotype (per Tesar et al.)	**Late-onset SCA-like**	**Typical GSS**	**GSS with areflexia and paresthesia**	**Typical GSS**	**CJD-like GSS**	**Typical GSS**	**Typical GSS with spastic paraparesis**
Areflexia		+ LE areflexia	+	+ LE areflexia	+ LE predominant		
Cognitive deficits		+ Impairment of verbal memory			+ MoCA (24/30)	++ MMSE 20/30	MMSE 24/30
Other examination features			Over time developed absent vertical gaze and pseudobulbar affect	Developed peri-oral twitching	CBS-like presentation, dystonic posturing in the hands		Spastic paraparesis Unclear role of previous +ive HTVL1 serology (but CSF normal cell count and chemistry, HTLV1 antibodies absent)
BARS at presentation	9	11	13	9	1.5	21	24.5
Imaging features							
MRI brain features	Mild T2 hyperintensities		Progressive cerebellar atrophy	Initially normal but progressive pontocerebellar atrophy	Progressive cerebellar atrophy	Cortical and cerebellar atrophy, subtle pallidal hypointensity	
MRI Cerebellar atrophy	−		+	+	+	+	
PET abnormalities					Cerebellar hypometabolism		
Other investigations							
Nerve conduction studies	Mild length-dependent sensory axonal peripheral neuropathy	−	−				

(Continues)

TABLE 1 *Continued*

Case	1	2	3	4*	5*	6	7
GSS Phenotype (per Tesar et al.)	**Late-onset SCA-like**	**Typical GSS**	**GSS with areflexia and paresthesia**	**Typical GSS**	**CJD-like GSS**	**Typical GSS**	**Typical GSS with spastic paraparesis**
EMG			Activation of right lower extremity muscles, absent tibial H reflexes, with normal F waves				
Vestibular testing				Decreased OKN, abnormal smooth pursuit, gaze-evoked nystagmus			
Genetic and related testing							
PRNP variant	c.392 G > A (p.Gly131Glu)	c.305 C > T (p.Pro102Leu)	c.305 C > T (p.Pro102Leu)	c.305 C > T (p.Pro102Leu)	N/A	c.305 C > T (p.Pro102Leu)	c.305 C > T (p.Pro102Leu)
Codon 129 enotype	129 M(V)	N/A	129 M(V)	N/A	N/A	N/A	129 V(V)
CSF 14–3-3	N/A	N/A	N/A	N/A	Negative	N/A	
Neuropathology			+				

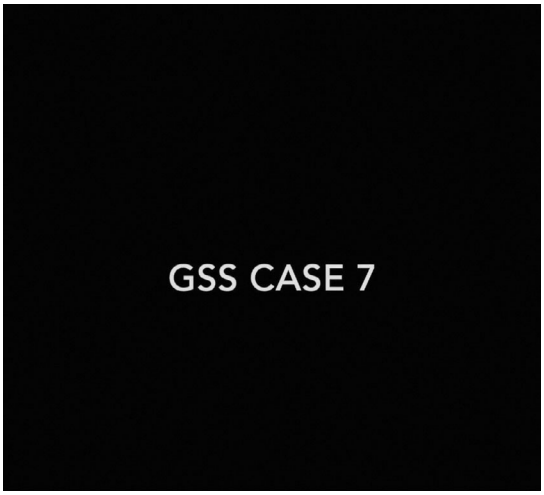
The codon 129 genotype is presented as cis if before parentheses and trans if in parentheses.
*Denotes siblings.
Abbreviations: F, female; M, male; UE, upper extremity; LE, lower extremity; BARS, Brief Ataxia Rating Scale; PET, positron emission tomography; EMG, electromyography; CSF, cerebrospinal fluid; SCA, spinocerebellar ataxia; MoCA, Montreal Cognitive Assessment; MMSE, Mini Mental State Examination, CBS, corticobasal syndrome; OKN, optokinetic nystagmus; N/A, not available.



Video 1. Examination of Case 1 at age 75. The video illustrates several features of the cerebellar motor syndrome, including cerebellar dysarthria, oculomotor features (saccadic pursuits, horizontal end-gaze nystagmus, hypermetric saccades), reasonably symmetric upper and lower extremity appendicular ataxia but a very subtle, almost normal gait disorder with intact ability to perform tandem gait (although her gait progressed over time).
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13976

in lower extremity muscles, absent tibial H-reflexes, and normal F-waves. MRI brain revealed progressive cerebellar atrophy **(**Fig. 2D–G**)**. At her last assessment at age 51 (BARS 27/30), she had absent vertical gaze, slow saccades, dysarthria, severe dysmetria and flaccid paraplegia. Exome sequencing revealed the p.P102L variant in *PRNP*. She died shortly after; an autopsy was performed.

Video 2. Examination of Case 6 at age 40. The video illustrates features of the cerebellar motor syndrome, including saccadic pursuits, slight horizontal end-gaze nystagmus, upper and lower extremity appendicular ataxia and a considerable gait disorder, requiring assistance, which was both ataxic and spastic.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13976



Video 3. Examination of Case 7 at age 31. The video illustrates features of the cerebellar motor syndrome, including saccadic pursuits, slight horizontal end-gaze nystagmus and moderate bilateral upper extremity dysmetria and overshoot on finger chase.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13976

Case 4

This woman noted imbalance at age 54, with progression resulting in multiple falls. She was of French Canadian/Italian descent. Family history (Fig. 1D) revealed a father with early-onset dementia and balance difficulties, and a brother with ataxia, dementia and parkinsonism. Examination at age 56, revealed oculomotor abnormalities, dysarthria, appendicular dysmetria and gait ataxia (BARS 9/30). Lower extremity reflexes were hypoactive. Extensive laboratory workup, including CSF, EEG and EMG were normal. Vestibular testing revealed decreased OKN, abnormal smooth pursuit, and gaze-evoked nystagmus. Neuroimaging revealed progressive cerebellar and brainstem atrophy (Fig. 2H–K). An ataxia panel identified a variant of unknown significance in the *ITPR1* gene (p.R1532Q); targeted *PRNP* gene sequencing revealed the p.P102L variant. She died at age 59, following hospice care.

Case 5

This man (brother of Case 4) noted imbalance at age 49, impairing exercise. He developed difficulties in handwriting, urinary urgency and neuropsychiatric changes, including cognitive decline and loss of empathy. He is the brother of Case 4 (Fig. 1D). Examination at age 52, revealed cognitive

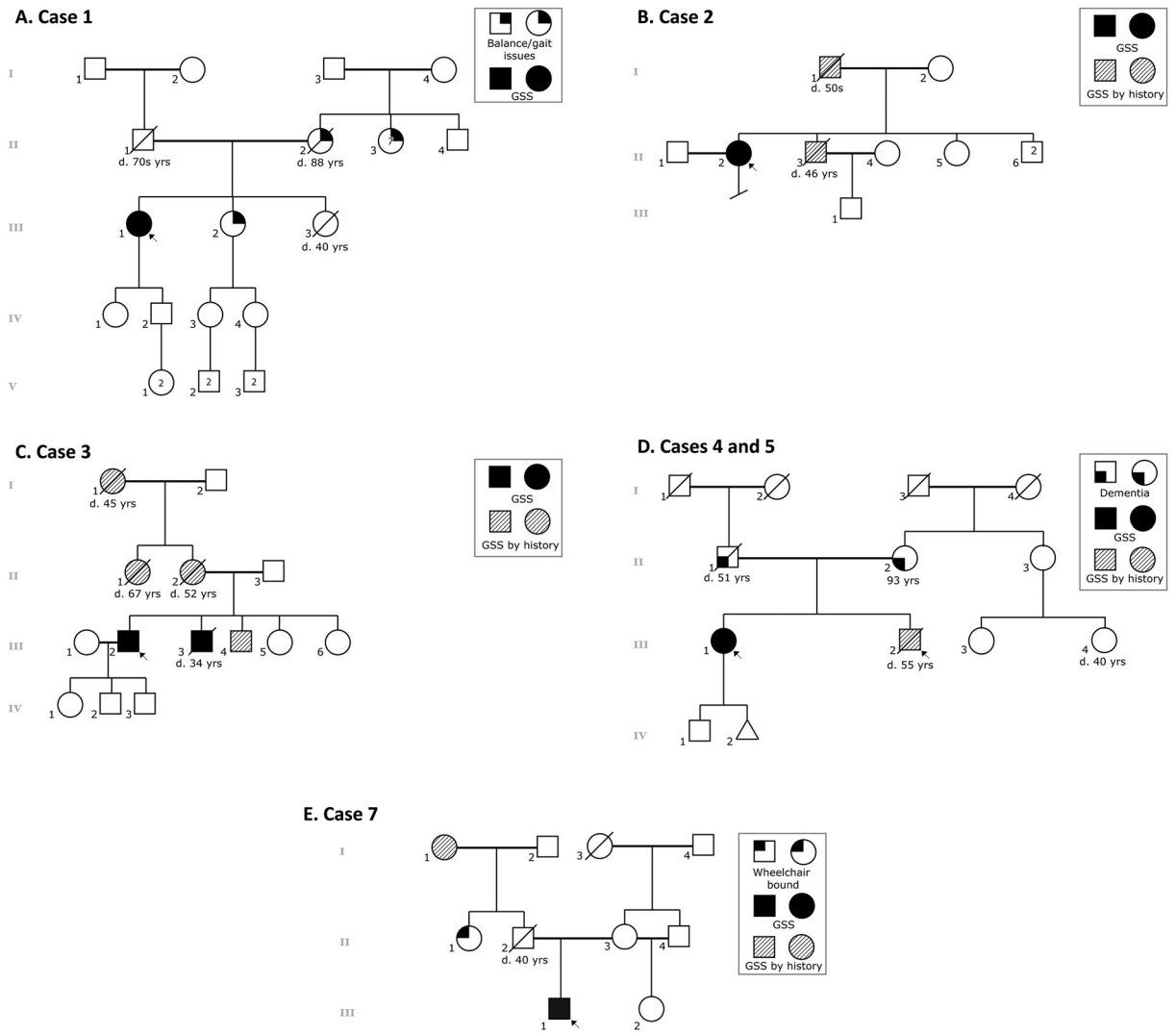
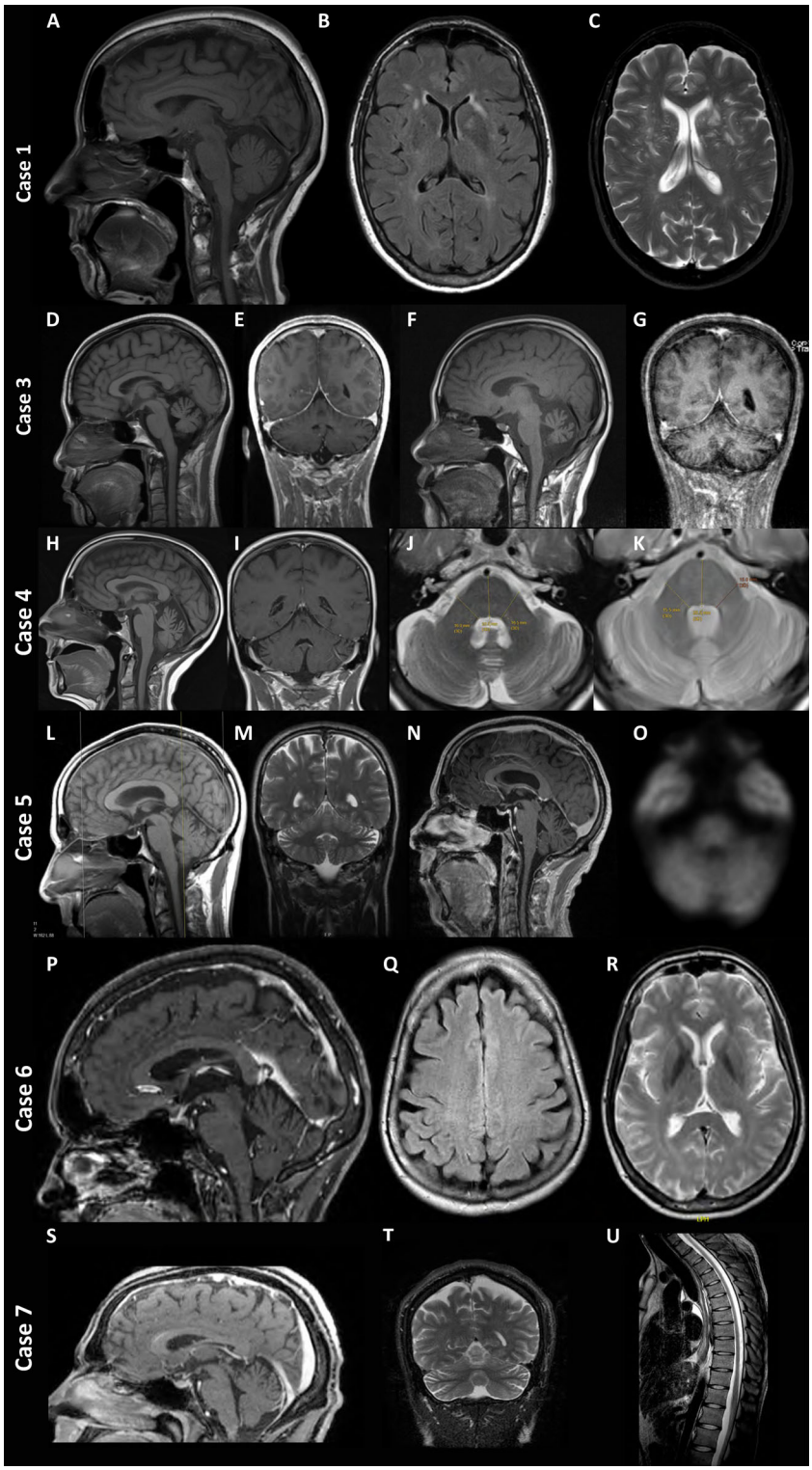


Figure 1. Pedigrees of Cases. (**A**) Pedigree for Case 1. There are several maternal family members with late-onset balance problems. The patient's mother had slowly worsening balance and dizziness in her 70s, and 7 maternal aunts had unexplained falls late in life (60s–70s), all with slow symptomatic progression. The patient's sister had balance problems, but her situation was complicated by a large stroke, without clear progression and hence may not be affected. (**B**) Pedigree for Case 2. There are several maternal family members with ataxia and cognitive symptoms in their 30s/40s, including the mother, maternal uncle, and maternal grandfather. His mother had progressive ataxia and dementia, dying at age 45 in a psychiatric ward, and a maternal aunt died of similar symptoms at age 67, although only his brother had positive genetic confirmation for GSS and had autopsy confirmation. Another brother had symptoms of GSS by history, including insomnia, poor memory, and some shaking of the extremities and unsteadiness of gait. (**C**) Pedigree for Case 3. The patient's father developed balance problems in his 40s and gradually developed paralysis in his 50s and died shortly thereafter (<10 years disease duration). The patient's brother had symptoms suggestive of GSS at age 32, with cognitive impairment, developing gait difficulties at age 35, becoming wheelchair-bound at age 40, anarthric by age 42/43, with dystonic posturing, and incontinent of both urine and feces. He died at age 46. (**D**) Pedigree for Cases 4 and 5. The patient's father had symptoms suggestive of GSS, with early-onset dementia (diagnosed as Alzheimer's disease) and unclear reports of balance difficulties who died at age 51; mother with late-onset Alzheimer's disease (alive in her 90s). Case 4 was genetically diagnosed with GSS and Case 5 (her brother), had classical symptoms of GSS but was not genetically diagnosed. (**E**) Pedigree for Case 7. The patient's father died at age 40, which may have concealed illness and his paternal aunt was wheelchair bound pf unclear cause. His paternal grandmother had symptoms highly suggestive of GSS, with dysarthria and lower limb spasticity. *Pedigree for Case 6 is not shown as the patient was adopted and therefore family history is unknown.*

dysfunction (MoCA 24/30), subtle cerebellar oculomotor findings, gait ataxia (BARS 1.5/30), and hypoactive/absent reflexes. Extensive laboratory workup included normal EEG, EMG and CSF, including autoimmune/paraneoplastic panel, 14-3-3 and tau levels. Brain MRI was unremarkable. CT positron emission tomography (PET) showed hypometabolism in the bilateral cerebral hemispheres and relative striatal hypometabolism (Fig. 2L–O). At age 54, symptoms had progressed, with



(Figure legend continues on next page.)

dysphagia, paucity of speech, right hemi-spasticity, a left parietal drift, appendicular and gait ataxia, requiring a walker (BARS 15.5/30). He died at age 55, following hospice care. Genetic testing was not possible. He was clinically diagnosed with GSS, given presentation and family history (Case 4).

Case 6

This woman developed imbalance at age 37. Family history is unknown, as she was adopted. She reported painful stiffness in her legs, forgetfulness and labile mood. Examination at age 40 (Video 2), revealed fluent speech and cognitive impairment (Mini Mental State Examination [MMSE] 20/30), dysarthria, oculomotor, appendicular and gait ataxia, with gait scissoring, requiring a walker (BARS 21/30). There was lower extremity spasticity and diffuse hyperreflexia, with mute plantar responses. Neuroimaging demonstrated cortical and cerebellar atrophy with discrete pallidal/dentate T2 hypointensities (Fig. 2P–R). Extensive laboratory work-up, including CSF studies was unrevealing. Genetic testing identified the p.P102L *PRNP* variant.

Case 7

This man first noticed gait difficulties at age 26, while playing soccer. He was of Brazilian descent. Family history (Fig. 1E) revealed dysarthria and leg spasticity in his paternal grandmother and gait difficulties in his aunt; his father died young at age 40, after a stroke. Symptoms progressed, becoming wheelchair-bound at age 29. Initial investigations suggested HTLV-1 tropical spastic paraparesis based on positive serum antibodies (CSF negative). Examination at age 31 (Video 3), revealed dysarthria, end-gaze nystagmus and upper extremity dysmetria. Lower extremities were spastic, hyperreflexic and paraparetic (MRC 3/5 bilaterally). BARS was 24.5/30 and MMSE 22/30. Neuroimaging demonstrated slight global cerebellar atrophy and thinning of the thoracic spinal cord (Fig. 2S–U). Exome sequencing identified the p.P102L *PRNP* variant.

Pathological Findings (Case 3)

Autopsy of Case 3 (Fig. 3) on gross assessment revealed moderate cerebellar atrophy, with unremarkable white matter and deep nuclei. Cerebral hemispheres were symmetrical, brainstem and basal ganglia were unremarkable. Cerebellar microscopic assessment demonstrated patchy loss of Purkinje cells with focal torpedoes and very mild patchy spongiform change in the molecular layer, with marked myelin loss in the white matter. The substantia nigra was well-pigmented, without Lewy bodies or inclusions. There was mild neuronal loss and gliosis in the basis pontis and inferior olivary nucleus. There were abundant prion plaques in the cerebellum, hippocampus, amygdala and neocortex, with severe spongiform change in the parietal lobules. Tissue was provided to the NPDPSC and immunoblot revealed abnormal protease resistant prion protein (PrPSc 7-8kD). Immunohistochemistry (Fig. 3D) with 3F4 antibody staining revealed unicentric and multi-core PrP plaques that are typically seen in GSS. Western blot (Fig. S1) using 3F4 antibody demonstrated protease-resistant low weight molecular bands (~7–8 kDa) typically observed in GSS.

Discussion

GSS is a rare inherited neurodegenerative disease. General clinical clues pointing to GSS are an autosomal dominant pattern of inheritance of ataxia, rapid progression and early development of dementia, although there is wide phenotypic overlap with other genetic prion diseases.[11] In addition to the classical presentation of ataxia and dementia, there are rare cases which can mimic a hereditary spasticity paraplegia (HSP) in the earlier stages,[12] while progressive weakness or neuropathic features (Tesar Type 2 can also be seen in genetic CJD[13]) may result in a misdiagnosis of motor neuron disease or a genetic amyotrophic lateral sclerosis/dementia syndrome.[14] Additional movement disorders include myoclonus, and rapidly progressive dystonia parkinsonism has been reported.[15] In contrast, dominantly-inherited spinocerebellar ataxias (SCAs) have slow disease progression.[16] A subacute/rapid progression can also be seen in paraneoplastic/autoimmune neurological disorders, neoplasia, central nervous system infection, and rarely toxic/metabolic causes, which should be excluded.[11] Sporadic CJD presents similarly but has a more rapid disease progression and is the main non-genetic differential. Multiple system atrophy of the cerebellar type, has a later onset, and is more slowly progressive, with characteristic pontocerebellar atrophy.[17]

(Figure legend continued from previous page.)

Figure 2. MRI imaging for Cases 1, 3, 4, 5, 6 and 7. Case 1: MRI Brain at age 74. (**A**) Mid-sagittal T1, (**B**) Axial T2 fluid-attenuated inversion recovery (FLAIR), (**C**) Axial T2. No cerebellar or brainstem atrophy, minimal cerebral atrophy, white matter hyperintensities, dilated perivascular spaces in basal ganglia and diffusion-weighted imaging is normal (not shown). Case 3: MRI Brain at age 44 (**D**/**E**) and age 49 (**F**/**G**). (**D** and **F**) Mid-sagittal T1, (**E** and **G**) Coronal Magnetization Prepared Rapid Gradient Echo (MPRAGE). There is progressive cerebellar atrophy and diffusion weighted imaging is normal (not shown). Case 4: MRI Brain at age 55 with sagittal T1 (**H**), coronal T1 (**I**) and axial T2 (**J**) revealing mild midline-predominant cerebellar atrophy; at age 56 with axial T2 (**K**), showing progressive cerebellar and middle cerebellar peduncle atrophy (note decreasing middle cerebellar peduncle diameters). Case 5: MRI Brain at age 51 with sagittal T1 (**L**) and coronal T2 (**M**) sequences, revealing subtle cerebellar hemispheric trophy; at age 52 revealing slight progression of midline cerebellar atrophy on sagittal T1 BRAVO post-contrast imaging (**N**); and positron emission tomography (PET) demonstrating cerebellar hypometabolism (**O**). Case 6: MRI Brain at age 40 with axial FLAIR (**P**), sagittal T1 with contrast (**Q**) and axial T2 (**R**) sequences. There is slight cortical and cerebellar atrophy, and pallidal hypointensity. Case 7: MRI Brain at age 31 with sagittal T1 (**S**), coronal T2 (**T**); and thoracic spine MRI T2 (**U**) sequences. In the brain, there is slight cerebellar atrophy and spinal cord imaging reveals thinning of the thoracic cord.

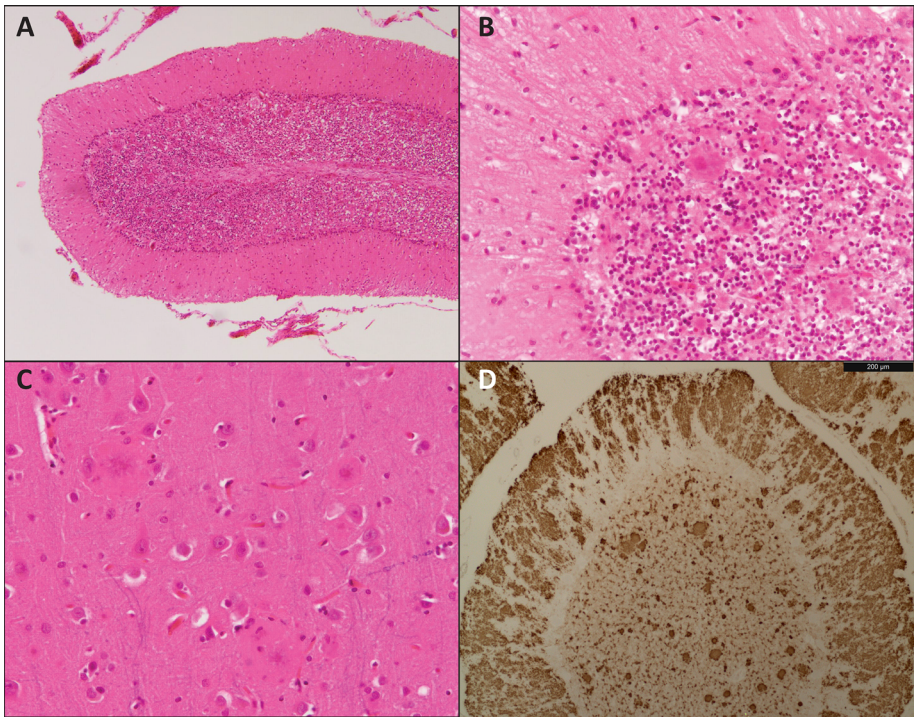


Figure 3. Case 3 neuropathology revealing classic signs of prion disease. Case 3 histological slides. (**A**) Cerebellar cortex (10× original magnification; Luxol H&E staining) demonstrating extensive loss of Purkinje cells with prominent Bergmann gliosis. There is minimal spongiform change evident in the molecular layer, although it is moderately attenuated, consistent with the depletion of Purkinje cells. The folial white matter is also depleted, suggesting loss of both input and output fibers associated with the cerebellar cortex. (**B**) Cerebellar cortex (40× original magnification; Luxol H&E staining) demonstrating prion plaques in the granule cell layer, as well as the extensive loss of Purkinje cells with prominent Bergmann gliosis. The attenuation of the molecular layer is well seen, with individual dendrites visible, in an abnormal manner. (**C**) Cerebral cortex (40× original magnification; Luxol H&E staining) demonstrating multiple prion plaques. There is minimal spongiform change present. (**D**) Cerebellar cortex immunohistochemistry (3F4 staining) demonstrating unicentric and multi-core prion plaques.

This case series illustrates the clinical heterogeneity in this devastating disorder. Case 1 represents a highly atypical presentation of GSS, with a much milder course and a much slower rate of progression, mimicking a dominantly-inherited, late-onset pure SCA. Case 2 had a typical GSS presentation (Tesar[4] Type 1), with some overlap with Tesar Type 2 (pain, paresthesias and lower extremity areflexia). Case 3 had severe, progressive leg weakness, consistent with GSS with areflexia and paresthesia (Tesar Type 2). The appendicular dysmetria principally affects the lower extremities in these cases. Case 4 was also typical (Tesar Type 1), but her brother (Case 5) had rapid progression, compatible with a CJD-like presentation (Tesar Type 3). Cases 6 and 7 had a presentation compatible with Tesar Type 1, but had additional pyramidal signs, with spastic paraparesis, mimicking a complex HSP, a rare presentation of GSS[12]. There were typical autopsy features of GSS in Case 3.[2]

Although GSS has a typical onset in the 30s–50s, rare late-onset cases exist. This late-onset presentation (Case 1) had a novel p.G131E *PRNP* variant, classified as likely pathogenic by American College of Medical Genetics and Genomics criteria, considering the previously reported pathogenic variant in the same codon (p.G131V), allele frequency and clinical phenotype. Previously published cases with the p.G131V variant presented at age 42 (death age 51),[18] 36 (death age 52),[19] and 43 (death age 45),[20] all with early dementia and later onset of ataxia. Case 1 had initial gait deterioration largely after exertion, progressed very slowly and does not have current signs of cognitive impairment. This suggests a new, much milder phenotype, expanding Tesar's phenotypic classification.[4] We postulate that the change to glutamic acid instead of valine in this codon may confer a milder disease phenotype. Whether the p.M129V polymorphism has any specific effect on the p.G131V mutation is unclear, although it is a known risk factor for prion disease.[10] This again illustrates different phenotypes arising from different variants within the same gene.[21] Factors influencing clinical heterogeneity include incomplete penetrance, variable gene expression and pleiotropy, involving both genetic and epigenetic factors,[21] which are particularly relevant in ultra-rare disorders such as genetic prion diseases.[11]

All GSS cases developed cerebellar ataxia during their disease course. Intriguingly, even siblings (Cases 4/5) had distinct presentations, suggesting phenotypic modifiers, as described in other

genetic prion diseases.[22] Case 3 developed vertical gaze palsy, which is a rare presentation in CJD-like GSS[23] but can also be seen in sporadic[24] and familial CJD[25] but evokes a differential diagnosis including Niemann-Pick disease type C or other PSP-mimics.[24] We also describe novel imaging findings, with Case 6 demonstrating pallidal hypointensity on T2 brain imaging. The nature of these pallidal changes is unclear, however there is data that the P102L variant may increase ferrireductase activity and therefore could result in accumulation of brain iron.[26,27]

Conclusions

Hereditary prion diseases are likely under-appreciated, particularly in late-onset, slowly progressive cases. This presentation, albeit uncommon, suggests that GSS should also be considered in the differential of late-onset SCAs. Our findings expand the genetic and phenotypic spectrum of GSS, highlighting the importance of genetic testing in ataxia.

Acknowledgments

We wish to acknowledge the GSS patients, as without whom, this work would not be possible. We also wish to thank Dr. Ignazio Cali at the National Prion Disease Pathology Surveillance Center for the production of the immunohistochemistry figure.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

C.S.: 1A, 1B, 1C, 3A, 3B
C.M.dG: 1C, 3B
S.S.: 1C, 3A, 3B
A.O.: 1C, 3B
F.F.: 1C, 3B
F.K.: 1C, 3B
R.M.G.B.: 1C, 3B
J.C.: 1C, 3B
B.A.: 1C, 3B
T.P.: 1C, 3B
M.F.: 1C, 3B
J.S.: 1A, 1B, 3B

Disclosures

Ethical Compliance Statement: This research was performed with approval of the ethics board of MassGeneral Brigham and the University of São Paulo, Brazil. Living patients have given written and informed consent for online publication of their videos and images. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

Funding Sources and Conflicts of Interest: This work was supported by the National Institutes of Health/National Institute of Neurological Disorders and Stroke K23NS118045 (CDS), CDC 1NU38CK000486 (BSA) and in part by the MINDlink Foundation. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the Previous 12 Months: CDS has performed scientific advisory for SwanBio Therapeutics and received research funding from Sanofi-Genzyme for a study in late-onset GM2 gangliosidosis. He has received financial support from SwanBio Therapeutics, Encora Therapeutics, Sanofi-Genzyme, Biogen, and Biohaven for the conduct of clinical trials and received honoraria from the International Parkinson and Movement Disorder Society, American Academy of Neurology and Oakstone CME. He has received grant support from the National Institutes of Health K23 NS118045-03. SRS has performed scientific advisory for Praxis Precision Medicines and Iota Biosciences. He has received grant support from the NIH R25 NS089450-06 and Parkinson Foundation. BA has received research funding from CDC, NIH, CJD Foundation, Ionis, and Alector. He has provided consultation for Ionis, Acadia and Sangamo, as well as being the Medical Director for the CJD Foundation. JDS is site PI for Biohaven Pharmaceuticals clinical trials NCT03701399, NCT02960893 and NCT03952806; receives royalties from Oxford University Press, Elsevier, MacKeith Press, and Springer; and is the inventor of the Brief Ataxia Rating Scale, Cerebellar Cognitive Affective/Schmahmann Syndrome Scale, the Patient Reported Outcome Measure of Ataxia, and the Cerebellar Neuropsychiatry Rating Scale which are licensed to the General Hospital Corporation. CMdG, FF, FK, RMGB, JYC, TP and MF report no relevant disclosures. ■

References

1. Kang MJ, Suh J, An SS, Kim S, Park YH. Pearls & oy-sters: challenging diagnosis of Gerstmann-Sträussler-Scheinker disease: clinical and imaging findings. *Neurology* 2019;92(2):101–103. https://doi.org/10.1212/wnl.0000000000006730.
2. Webb TE, Poulter M, Beck J, et al. Phenotypic heterogeneity and genetic modification of P102L inherited prion disease in an international series. *Brain* 2008;131(Pt 10):2632–2646. https://doi.org/10.1093/brain/awn202.
3. Appleby BS, Shetty S, Elkasaby M. Genetic aspects of human prion diseases. *Front Neurol* 2022;13:1–10. https://doi.org/10.3389/fneur.2022.1003056.
4. Tesar A, Matej R, Kukal J, et al. Clinical Variability in P102L Gerstmann-Sträussler-Scheinker Syndrome. *Ann Neurol* 2019;86(5):643–652. https://doi.org/10.1002/ana.25579.
5. Yoshimura M, Yuan JH, Higashi K, et al. Correlation between clinical and radiologic features of patients with Gerstmann-Sträussler-Scheinker syndrome (Pro102Leu). *J Neurol Sci* 2018;391:15–21. https://doi.org/10.1016/j.jns.2018.05.012.
6. Schmitz M, Villar-Piqué A, Hermann P, et al. Diagnostic accuracy of cerebrospinal fluid biomarkers in genetic prion diseases. *Brain* 2022;145(2):700–712. https://doi.org/10.1093/brain/awab350.

7. Rhoads DD, Wrona A, Foutz A, et al. Diagnosis of prion diseases by RT-QuIC results in improved surveillance. *Neurology* 2020;95(8):e1017–e1026. https://doi.org/10.1212/wnl.0000000000010086.

8. Schmahmann JD, Gardner R, MacMore J, Vangel MG. Development of a brief ataxia rating scale (BARS) based on a modified form of the ICARS. *Mov Disord* 2009;24(12):1820–1828. https://doi.org/10.1002/mds.22681.

9. Santini S, Claude JB, Audic S, Derreumaux P. Impact of the tail and mutations G131V and M129V on prion protein flexibility. *Proteins* 2003;51(2):258–265. https://doi.org/10.1002/prot.10348.

10. Jones E, Hummerich H, Viré E, et al. Identification of novel risk loci and causal insights for sporadic Creutzfeldt-Jakob disease: a genome-wide association study. *Lancet Neurol* 2020;19(10):840–848. https://doi.org/10.1016/s1474-4422(20)30273-8.

11. Zerr A, Schmitz M. Genetic prion disease. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle; 1993–2023 Available from: https://www.ncbi.nlm.nih.gov/books/NBK1229/. 2003 Mar 27 [Updated 2021 Jan 7].

12. Ishizawa K, Mitsufuji T, Shioda K, et al. An autopsy report of three kindred in a Gerstmann-Sträussler-Scheinker disease P105L family with a special reference to prion protein, tau, and beta-amyloid. *Brain Behav* 2018;8(10):e01117. https://doi.org/10.1002/brb3.1117.

13. Stephen CD, Schaefer PW, Appleby BS, Oakley DH. Case 5-2022: a 65-year-old woman with rapidly progressive weakness in the right arm and recurrent falls. *N Engl J Med* 2022;386(7):674–687. https://doi.org/10.1056/NEJMcpc2115852.

14. Geschwind MD. Rapidly progressive dementia. *Continuum (Minneap Minn)* 2016;22(2 Dementia):510–537, 537. https://doi.org/10.1212/con.0000000000000319.

15. Umeh CC, Kalakoti P, Greenberg MK, et al. Clinicopathological correlates in a PRNP P102L mutation carrier with rapidly progressing parkinsonism-dystonia. *Mov Disord Clin Pract* 2016;3(4):355–358. https://doi.org/10.1002/mdc3.12307.

16. Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. *Nat Rev Dis Primers* 2019;5(1):24. https://doi.org/10.1038/s41572-019-0074-3.

17. Claassen DO. Multiple system atrophy. *Continuum (Minneap Minn)* 2022;28(5):1350–1363. https://doi.org/10.1212/con.0000000000001154.

18. Panegyres PK, Toufexis K, Kakulas BA, et al. A new PRNP mutation (G131V) associated with Gerstmann-Sträussler-Scheinker disease. *Arch Neurol* 2001;58(11):1899–1902. https://doi.org/10.1001/archneur.58.11.1899.

19. Jansen C, Parchi P, Capellari S, et al. A second case of Gerstmann-Sträussler-Scheinker disease linked to the G131V mutation in the prion protein gene in a Dutch patient. *J Neuropathol Exp Neurol* 2011;70(8):698–702. https://doi.org/10.1097/NEN.0b013e3182270c54.

20. Alshaikh JT, Qin K, Zhao L, Mastrianni JA. A novel PRNP-G131R variant associated with familial prion disease. *Neurol Genet* 2020;6(4):e454. https://doi.org/10.1212/nxg.0000000000000454.

21. Magrinelli F, Balint B, Bhatia KP. Challenges in Clinicogenetic correlations: one gene - many phenotypes. *Mov Disord Clin Pract* 2021;8(3):299–310. https://doi.org/10.1002/mdc3.13165.

22. Cracco L, Appleby BS, Gambetti P. Fatal familial insomnia and sporadic fatal insomnia. *Handb Clin Neurol* 2018;153:271–299. https://doi.org/10.1016/b978-0-444-63945-5.00015-5.

23. Paul AM, Mu W, Butala A, Green KE. Pearls & oy-sters: deep phenotyping of abnormal eye movements advances the detection of Gerstmann-Sträussler-Scheinker syndrome. *Neurology* 2022;99(21):957–961. https://doi.org/10.1212/wnl.0000000000201321.

24. Lloyd-Smith Sequeira A, Rizzo JR, Rucker JC. Clinical approach to Supranuclear brainstem saccadic gaze palsies. *Front Neurol* 2017;8:1–8. https://doi.org/10.3389/fneur.2017.00429.

25. Bertoni JM, Label LS, Sackelleres JC, Hicks SP. Supranuclear gaze palsy in familial Creutzfeldt-Jakob disease. *Arch Neurol* 1983;40(10):618–622. https://doi.org/10.1001/archneur.1983.04050090054008.

26. Wong BX, Duce JA. The iron regulatory capability of the major protein participants in prevalent neurodegenerative disorders. *Front Pharmacol* 2014;5:1–10. https://doi.org/10.3389/fphar.2014.00081.

27. Singh A, Haldar S, Horback K, Tom C, Zhou L, Meyerson H, Singh N. Prion protein regulates iron transport by functioning as a ferrireductase. *J Alzheimers Dis* 2013;35(3):541–552. https://doi.org/10.3233/jad-130218.

Supporting Information

Supporting information may be found in the online version of this article.

Figure S1. Western blot from Case 3 using 3F4 antibody. The Western blot reveals protease-resistant low weight molecular bands (~7–8 kDa) typically observed in GSS.