Pearls & Oy-sters: Deep Phenotyping of Abnormal Eye Movements Advances the Detection of Gerstmann-Sträussler-Scheinker Syndrome

Ashley M. Paul, MD, Weiyi Mu, ScM, Ankur Butala, MD,* and Kemar E. Green, DO*

Abstract
A 58-year-old previously healthy woman presents with 3 years of rapidly progressive ataxia, parkinsonism, dysautonomia, peripheral neuropathy, leg weakness, spasticity, hyperreflexia, and mild vertical-gaze palsy. She has a matrilineal family history of neurodegenerative diseases. She was initially postulated to have spinocerebellar ataxia or atypical parkinsonism with cerebellar features. However, on closer inspection, her abnormal extraocular eye movements suggested rare mimicking disorders such as prion disease as part of the differential diagnosis, requiring further evaluation. This case highlights how deep phenotyping can open new diagnostic considerations, inform additional workup, and yield the precise diagnosis of Gerstmann-Sträussler-Scheinker syndrome (GSS).

Pearls
- GSS is a rare autosomal dominant prion disease that clinically overlaps with atypical parkinsonism and hereditary spinocerebellar ataxias (SCAs).
- Deep phenotyping of extraocular movements can aid localization and increase the diagnostic accuracy of GSS in patients with parkinsonism and cerebellar mesocephalic oculomotor abnormalities.
- Although crucial, the absence of family history does not rule out GSS.

Oysters
- GSS is often not considered because of its clinical rarity—without the appropriate investigative workup, the diagnosis will be missed.
- Supportive diagnostic studies such as real-time quaking-induced conversion (RT-QuIC) may lack the typical findings seen in prion disease but do not exclude the diagnosis of GSS.
- Consider a second-tier genetic test such as whole-exome or genome sequencing, especially for complex or atypical cases that have initially negative ataxia gene panels.

Case Report
A 58-year-old woman presented to the clinic with 3 years of rapidly progressive gait dysfunction. She first noticed stumbling on uneven surfaces, followed by falls and clumsiness. Within 1 year, she had a rapid decline in coordination, forcing her resignation from work. Her gait progressively declined requiring a walker and then a wheelchair. Within 2 years, she developed slurred speech, difficulty swallowing, fatigue, mood changes, impaired multitasking, and tip-of-the-tongue phenomena. Associated motor symptoms included right hemibody rigidity and bradykinesia and lower limb weakness with spasticity. She had nonmotor symptoms of urinary incontinence, peripheral neuropathy, and vertigo but denied oscillopsia or diplopia. She was otherwise healthy and could scuba dive before symptom onset. Family history is notable for young-onset
neurodegeneration in both her mother and maternal grandmother in their 50s. Her mother died at age 57 years and was diagnosed with a rapidly progressive "Parkinson variant." Her grandmother died at age 58 years and was diagnosed with Alzheimer disease (AD) by autopsy (Figure 1A).

Examination of our patient showed truncal greater than limb ataxia, parkinsonism with asymmetric cogwheel rigidity and bradykinesia, right leg weakness with spasticity, and hyperreflexia. The eye movement range was full except for bilateral vertical gaze restriction that resolved with the vertical doll’s eye maneuver. Vestibular/ocular motor examination showed frequent square wave jerks (SWJs), gaze-evoked nystagmus with rebound, horizontal saccadic dysmetria, impaired vertical > horizontal smooth pursuits, absent vertical optokinetic nystagmus (OKN), and a mildly hyperactive horizontal (left gain = 1.2 and right gain = 1.5) vestibulo-ocular reflex (VOR) on video head-impulse testing. Video-oculography (VOG) testing revealed head shaking–induced left-beating nystagmus and positional-induced geotropic/upbeat nystagmus (Figure 2, Video 1 and Video 2). Her MRI showed mild volume loss of the superior cerebellum and pons without cortical ribboning on diffusion-weighted imaging (Figure 1B and C). An extensive workup, including serum and cerebrospinal fluid (CSF) analysis, ruled out neurologic paraneoplastic/autoimmune disorders, nutritional, infectious, or toxic etiologies. Her CSF showed elevated 14-3-3 protein tau, but RT-QuIC—used to detect misfolded prion protein—was negative. The electroencephalography was normal with no epileptiform discharges or lateralizing signs.

**Figure 1** Family Pedigree and MRI of the Brain

(A) Family history and pedigree (B) Sagittal T1 MRI of the brain with mild atrophy of the superior cerebellum and pons. (C) Axial DWI MRI of the brain and T2 FLAIR do not show evidence of cortical ribboning—a classic MRI finding in prion disease. No "hot cross bun" sign present that is sometimes seen with multiple system atrophy.
The initial suspicion was for SCA or atypical parkinsonism. A subsequent comprehensive ataxia gene panel was negative; however, whole-exome sequencing (WES) showed heterozygosity for a known pathogenic variant c.593T>C (p.F198S) and for homozygous c.385A>G (p.M129V) [genotype V/V] polymorphism in the prion protein (PRNP) gene. This mutation confirmed a diagnosis of GSS syndrome, an autosomal dominant hereditary prion disorder.

**Discussion**

Hereditary prion disease presents as 1 of the 3 phenotypes: GSS, Creutzfeldt-Jakob disease (CJD), or fatal familial insomnia (FFI). All 3 types can present with ataxia, myoclonus, pyramidal or extrapyramidal signs, and neuropsychiatric disorders with onset in the 5th or 6th decade. CJD is characterized by a rapid cognitive and motor decline that occurs over months with a median mortality of 6 months. GSS occurs earlier in life (35–50 years). It usually presents with ataxia, but other phenotypes can initially present with either dementia or paresthesia or follow a similar course to CJD. The survival rate can vary from 2 to 10 + years. In addition, the onset of FFI can include weight loss, sleep disorders, and dysautonomia with a median survival rate of 16 months. Although all 3 phenotypes present with elevated levels of 14-3-3 protein/tau on CSF analysis, RT-QuIC has superior sensitivity and specificity, especially in the evaluation of CJD. MRI classically shows cortical ribboning or signal changes in the caudate nucleus (on DWI or FLAIR)—particularly in CJD—but these findings can be absent in GSS and FFI. It is important to obtain a careful family history, but not be misled by vague clinical diagnoses of family members (such as “Parkinson variant”)—especially if they were not genetically confirmed. The neuropathologic features of both GSS and AD include amyloid deposition; in fact, there can be coexisting prion protein (PrP) amyloid and Aβ plaques seen in one individual. Unfortunately, the grandmother’s autopsy report was unavailable for neuropathologic correlation. GSS is especially challenging to diagnose because of phenotypic heterogeneity and variability in disease progression. Because the prevalence of GSS is 1–10 in 100,000,000, it is likely that physicians will consider more common ataxia syndromes over a rare prion disease.

Multiple neurologists who evaluated this patient suspected SCA syndrome—a reasonable initial consideration given the progression of symptoms, the findings of complex cerebellar ataxia with extrapyramidal features, and the fact that SCAs are...
more common. Yet, one must consider the complicated a-
ferent and efferent connections of the cerebellum to the
brainstem, thalamus, and cortex that make cerebellar local-
ization imprecise. Deep phenotyping of subtle oculomotor
findings on the patient’s examination—further elucidated
with VOG testing—revealed ocular motor cerebellar signs
(i.e., impaired smooth pursuit, gaze-evoked nystagmus, cen-
tral positional nystagmus, head shaking nystagmus, saccadic
dysmetria, etc.) in addition to supranuclear vertical gaze palsy.
These abnormalities in addition to her known progressive
cerebellar ataxia and parkinsonism localize to cerebellar
mesencephalic basal ganglia pathways and opens consider-
ations for alternative diagnoses not previously considered.

Yee et al. examined extraocular eye movements (EOMs) in a
large GSS family in Indiana to determine whether subtle ab-
normal EOMs could be early indicators of disease. Affected
family members had nystagmus, impaired smooth pursuit,
abnormal OKNs, and inability to suppress VORs with
family members had nystagmus, impaired smooth pursuit,
and supranuclear gaze palsy, a diagnosis of GSS
should be considered, even in the setting of a negative
diagnostic workup.

The incidence of GSS may be higher than what we know
due to misdiagnosis. Increased detection will slowly pave
the way for observation studies, clinical trials, and the
eventual discovery of disease-modifying therapy. It begins
with the astute clinician using deep phenotyping, localiza-
tion, and the sophisticated advancements of genetic testing
to find rare genetic diagnoses such as GSS.

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