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

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Abstract

A 58-year-old previously healthy woman presents with three 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. But 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.
- Though crucial, the absence of family history does not rule out GSS.

Oysters

- GSS is often not considered due to 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 three years of rapidly progressive gait dysfunction. She first noticed stumbling on uneven surfaces, followed by falls and clumsiness. Within one 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 two years, she developed slurred speech, difficulty swallowing, fatigue, mood changes, impaired multi-tasking, and tip-of-the-tongue phenomena. Associated motor symptoms included right hemibody rigidity and bradykinesia, and lower limb weakness with spasticity. She had non-motor symptoms of urinary incontinence, peripheral neuropathy, and vertigo but denied oscillopsia or diplopia. She was otherwise healthy and could scuba dive prior to 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’s variant.” Her grandmother died at age 58 years and was diagnosed with Alzheimer’s 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 exam 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 & right gain = 1.5) vestibulo-ocular reflex (VOR) on video head-impulse testing (vHIT). Video-oculography (VOG) testing revealed headshaking-induced left-beating nystagmus and positional-induced geotropic/upbeat nystagmus (Figure 2, Videos 1 and 2). Her MRI showed mild volume loss of the superior cerebellum and pons without cortical ribboning on diffusion-weighted imaging (Figure 1b and 1c). An extensive workup, including serum and cerebrospinal fluid (CSF) analysis, ruled out neurological 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 (EEG) was normal with no epileptiform discharges or lateralizing signs. 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 one of three phenotypes: GSS, Creutzfeldt-Jakob disease (CJD), or fatal familial insomnia (FFI). All three types can present with ataxia, myoclonus, pyramidal or extrapyramidal signs, and neuropsychiatric disorders with onset in the 5th or 6th decade.1 CJD is characterized by a rapid cognitive and motor decline that occurs over months with a median mortality of
GSS occurs earlier in life (35-50 years old). 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. Additionally, the onset of FFI can include weight loss, sleep disorders, and dysautonomia with a median survival rate of 16 months. While all three phenotypes present with elevated levels of 14-3-3 protein/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 neuropathological features of both GSS and AD include amyloid deposition; in fact, there can be co-existing Prion Protein (PrP) amyloid and Aβ plaques seen in one individual. Unfortunately, the grandmother’s autopsy report was unavailable for neuropathological correlation. GSS is especially challenging to diagnose due to phenotypic heterogeneity and variability in disease progression. Since 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 afferent and efferent connections of the cerebellum to the brainstem, thalamus, and cortex that make cerebellar localization imprecise. Deep phenotyping of subtle oculomotor findings on the patient’s exam—further elucidated with VOG testing—revealed ocular motor cerebellar signs (i.e., impaired smooth pursuit, gaze-evoked nystagmus, central 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 considerations for alternative diagnoses not previously considered.

Yee et al. examined extraocular eye movements (EOMs) in a large GSS family in Indiana to determine if subtle abnormal EOMs could be early indicators of disease. Affected family members had nystagmus, impaired smooth pursuit, abnormal OKNs, and inability to suppress VORs with fixation—all of which localize to the oculomotor vermis and flocculus of the cerebellum. Only three out of eleven studied at-risk individuals had subtle cerebellar findings. Similar to our patient, more advanced patients had vertical gaze palsy and square wave jerks which localize to the brainstem and might be seen in cases of atypical parkinsonism, such as the cerebellar types of both multiple systems atrophy (MSA) and progressive supranuclear palsy (PSP) in addition to common SCAs. While she could have been diagnosed with probable MSA per the established Movement Disorder Society clinical criteria, her vertical-gaze palsy and family history was suggestive of a tauopathy, such as PSP or mimicking disorder including Niemann-Pick disease type C, corticobasal degeneration, anti-iglon5 disease, prion diseases, Whipple’s Disease, Dentatorubral-pallidoluysian atrophy, among others. PSP with predominant cerebellar features (PSP-C) have been pathologically identified although is not included as a subtype in the 2017 Movement Disorder Society Criteria for PSP because it is a rare phenotype in Western populations. Nevertheless, PSP-C remained a diagnostic consideration. The negative RT-QuIC confounded the considerations of prion disease, as RT-QuIC has been shown to have higher diagnostic accuracy and reliability over 14-3-3 protein tau in prionopathies.
progressive cerebellar ataxia, parkinsonism, and supranuclear gaze palsy, a diagnosis of GSS should be considered, even in the setting of a negative seemingly thorough diagnostic workup.

Currently, the diagnosis of patients with parkinsonism and cerebellar disorders relies on expert opinion and is rarely identified on initial intake. Even with a multi-generation family history, only 30% of patients with cerebellar ataxia who are tested with an ataxia gene panel receive a genetic confirmation—this percentage rises to 50% when WES is added. Negative family history should not be contraindicative for genetic testing; many genetic disorders such as late-onset variations of metabolic disorders or de novo autosomal dominant disorders will not have any suggestive family history. GSS and other neurogenetic disorders can be considered as part of a broad differential when initial evaluation for reversible/treatable causes of neurodegeneration have been excluded and when deep phenotyping is more suggestive of a rarer entity as demonstrated by our case. WES is a cost and time-effective strategy to assess for thousands of disorders at once.

Our patient had a positive family history, but consider her negative spinocerebellar ataxia panel. We justified proceeding to whole-exome sequencing by noting that certain diagnostic possibilities—elucidated by deep phenotyping of eye movements—were not previously included. Our patient is also homozygous for the potentially modifying c.385A>G (p.M129V) [genotype V/V] polymorphism in PRNP. This polymorphism could be associated with a longer disease course up to 12 years, yielding valuable prognostic information for the patient and her children.

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, localization, and the sophisticated advancements of genetic testing to find rare genetic diagnoses such as GSS.

Figures:

Figure 1 Family pedigree and MRI brain. 1A. family history and pedigree 1B. Sagittal T1 MRI brain with mild atrophy of the superior cerebellum and pons. 1C. Axial DWI MRI 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 Systems Atrophy.
Figure 2 VOG. 2a. Gaze evoked nystagmus with rebound. Enlargement shows fast and slow phase of right beating nystagmus with right gaze. See Video 1. 2b. Square wave jerks (SWJs) seen in primary gaze. A sign of gaze holding deficit. See Video 2.

Key: LBN = left beating nystagmus; RBN = right beating nystagmus
Supplemental Videos:

Video 1 Gaze evoked nystagmus with rebound. 0-12 seconds: Mild LBN with left gaze; 12-16 seconds: Mild RBN (rebound nystagmus); 17-28 seconds: RBN with right gaze; 28 seconds to end: LBN (rebound nystagmus). See figure 2a.

Video 2 Frequent SWJs. Saccadic intrusions move the eye away and back to the point of fixation. See figure 2b.

Key: LBN = left beating nystagmus; RBN = right beating nystagmus; SWJs = square wave jerks.

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