CLINICAL/SCIENTIFIC NOTE OPEN ACCESS

Paroxysmal Ataxia

A Characteristic Feature of FGF14 Repeat Expansion (SCA27B)

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Abstract

Objectives

Paroxysmal ataxia is typically characterized by early-onset attacks of cerebellar ataxia. Late-onset cerebellar ataxia (LOCA) comprises a group of neurodegenerative disorders mainly characterized by adult-onset progressive cerebellar ataxia. A deep intronic expansion of a GAA triplet in the *FGF14* gene encoding fibroblast growth factor 14 has recently been identified as a frequent cause of LOCA.

Methods

We describe a patient with paroxysmal ataxia/dysarthria due to a *FGF14* repeat expansion and 3 affected family members.

Results

The 4 patients had paroxysmal ataxia/dysarthria occurring between 45 and 50 years as the initial manifestation of a *FGF14* repeat expansion. The index case was investigated in detail. We have provided a video showing one of her paroxysmal episodes that could be triggered by alcohol, coffee, exertion, emotion, or cigarette smoking. Brain MRI revealed mild cerebellar atrophy, and oculography showed a subclinical downbeat nystagmus. Treatment with acetazolamide resulted in remarkable improvement.

Discussion

Paroxysmal dysarthria/ataxia should prompt the clinician to test for *FGF14* repeat expansion/SCA27B, especially when the paroxysmal attacks are associated with late-onset cerebellar ataxia and/or a family history consistent with a dominant disorder.

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Video

Introduction

Paroxysmal ataxia is a rare movement disorder typically characterized by early-onset attacks of cerebellar ataxia that can last from a few seconds to several days.[1] Duration of the attacks and triggering factors mostly depend on the underlying cause. Ataxia is often associated with additional manifestations during attacks, such as dysarthria, tremor, vertigo, nausea, diplopia, dystonia, hemiplegia, headache, and tinnitus.

Late-onset cerebellar ataxia (LOCA) comprises a group of neurodegenerative disorders mainly characterized by adult-onset progressive cerebellar ataxia.[2] For most patients with LOCA, the cause usually remains unknown despite thorough etiologic assessment including extensive genetic investigations. A deep intronic expansion of a GAA triplet in the *FGF14* gene encoding fibroblast growth factor 14 has recently been identified as a frequent cause of LOCA (spinocerebellar ataxia

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27B, SCA27B) with a frequency ranging from 10% to 61% in several LOCA cohorts from various countries.[3-5] The transmission is autosomal dominant with a pathologic threshold above 250 GAA.[3,6,7]

Of interest, paroxysmal ataxia can be part of the phenotype in patients with LOCA. We describe a family with LOCA and paroxysmal ataxia due to a *FGF14* repeat expansion.

A 51-year-old woman was seen in our hospital with a 6-year history of paroxysmal dysarthria-ataxia (Video 1, Table 1). Her episodes lasted between 10 minutes and 2 hours and were characterized by dysarthria, gait ataxia, dizziness, and writing difficulties. Their frequency gradually increased over time up to 1 or 2 attacks per day. The patient described typical triggers such as tobacco, coffee, tea, alcohol, emotion, and prolonged physical exercise. Interictal examination was normal with a Scale for Assessment and Rating of Ataxia (SARA) score of 0. During a mild paroxysmal episode, we were able to perform an ictal examination and found a SARA score of 2. The patient showed no signs of dysautonomia (especially no orthostatic hypotension or low urinary tract symptoms) and normal pallesthesia and reflexes. She described a fluctuating "sensation of brain fog" in the absence of cognitive impairment.

Brain MRI of the patient showed slight cerebellar atrophy predominating on the vermis. Video 1 oculography eye tracking showed an asymptomatic low-amplitude downbeat nystagmus increased by head shaking maneuvers, increased square wave jerks, jerky pursuit with a downward predominance, and variable saccadic gain with a tendency to hypometria. Electromyogram and spinal cord MRI were normal. Extensive workup exploring other causes of cerebellar syndrome was negative. *FGF14* testing demonstrated an expanded allele (>450 repeats, abnormal threshold ≥250).[3-5] Treatment with acetazolamide 500 mg/d resulted in a major decrease in the frequency and severity of attacks. Treatment with 4-aminopyridine was not tested.

The patient's mother, grandmother, and sister had similar manifestations around the same age. In addition, her mother developed permanent cerebellar manifestations from age 85 years in addition to the paroxysmal attacks (Video 1, Table 1).

Discussion

A *FGF14* repeat expansion has been identified in patients with unexplained LOCA of various origins, especially in Europe and North America[3,4,6,7] (eTable 1, links.lww.com/NXG/A657). Transmission of this expansion is autosomal dominant, although sporadic cases represent approximately 40% of the cases, probably reflecting incomplete penetrance or anticipation.[3,4,6,7] The main clinical features can be permanent ataxia, paroxysmal ataxia, or a combination thereof. As in our patients, paroxysmal attacks are typically characterized by diplopia, vertigo, dysarthria, and impaired walking lasting from a few minutes to a few days and represent the initial manifestation of the disease in 12%–73% of the cases.[3,4,7] Frequent triggering factors are alcohol and exertion.[3,4,6,7] Our report illustrates that various additional triggering factors can be observed at an individual level such as emotion, cigarette smoking, or tea/coffee consumption. The 4 members of the family reported here had paroxysmal ataxia as the initial manifestation of the disease, with an earlier onset compared with most patients reported in the literature.[3,4] Onset is usually between 50 and 60 years and tends to be earlier when paroxysmal ataxia is the initial manifestation of the disease and when the size of the expansion is greater.[4-7] The high expansion size (>450) and the paroxysmal presentation may thus account for the relatively early onset observed in our family. Of interest, one of our patients had purely episodic paroxysmal dysarthria-ataxia for more than 10 years. Patients (including 3 of the patients we report here) sometimes complain of a brain fog sensation without associated cognitive dysfunction.[8] Additional neurologic manifestations (not observed in our patients) can comprise spasticity, hypopallesthesia, and dysautonomia (mostly in the form of urinary dysfunction).[3,4,6-8]

Cerebral MRI often shows isolated cerebellar atrophy predominantly in the vermis, as observed in our index case.[3,4,6,7,9] Although SCA27B is not associated with a specific oculomotor profile, eye movement disorders are frequent, especially with a high prevalence of downbeat (as in our patient) or gaze-evoked nystagmus and diplopia (eTable 1, links.lww.com/NXG/A657). Of interest, interictal eye tracking in our index patient with paroxysmal ataxia revealed slight oculomotor abnormalities indicative of interictal cerebellar dysfunction and more specifically of a vestibulocerebellum impairment. Some patients have been reported to display associated sensory motor neuropathy ascertained by EMG, which was not found in our family.[3,4,6,7] As observed in the patients of our family, the disease is of slow progression with a mean change of 0.2–0.4 points per year on the SARA scale,[6,7] regardless of the clinical form of the disease and expansion size. SARA scores can remain moderate 20 years after disease onset in some patients,[7] and this does not seem to be influenced by the number of expansions.[5,10] Uncontrolled studies indicate that treatment with acetazolamide (as in our patient) or 4-aminopyridine may reduce the number and intensity of paroxysmal ataxia attacks as well as permanent cerebellar manifestations.[7,8,11]

In addition to LOCA, paroxysmal dysarthria/ataxia should prompt the clinician to test for *FGF14* repeat expansion/SCA27B, especially when paroxysmal attacks are associated with a late-onset cerebellar ataxia and/or a family history consistent with a dominant disorder. Brain MRI and video oculography eye tracking can provide additional diagnostic clues. This is important for clinical practice because treatments with acetazolamide or 4-aminopyridine can be remarkably effective in this context, at least for some patients.

Table 1 Characteristics of the Patients (in This Report)

Characteristics	Index case	Grandmother	Mother	Sister
Inheritance				
Familial	Yes	ND	Yes	Yes
Sporadic	No	ND	No	No
No of GAA expansions	485	ND	450	500
Paroxysmal ataxia				
Onset with episodic ataxia	Yes	Yes	Yes	Yes
Age at onset of paroxysmal episodes (y)	45 y	45 y	50 y	45 y
Triggering factors	Alcohol, tobacco, coffee, tea, emotion, fatigue, exertion	Emotion, Fatigue	Emotion, Fatigue	Alcohol, exertion
Duration of episodes	10 min to 2 h	ND	10 min to 2 h	1 min to 1 h
Frequency of episodes	Daily to monthly occurrence	ND	ND	Daily to monthly occurrence
Paroxysmal cerebellar manifestations				
Ataxic dysarthria	Yes	Yes	Yes	Yes
Gait ataxia	Yes	Yes	Yes	Yes
Vertigo or dizziness	Yes	ND	Yes	Yes
Postural tremor	Yes	ND	No	Yes
Permanent ataxia				
Age at onset of permanent ataxia (y)	ND	ND	ND	ND
Cerebellar manifestations				
Cerebellar dysarthria	No	Yes	Yes	No
Gait ataxia	No	Yes	Yes	Yes
Vertigo or dizziness	No	ND	Yes	No
Postural tremor	No	ND	Yes	No
Intention tremor	No	ND	Yes	Yes
Rest tremor	No	ND	No	No
Nystagmus				
Downbeat nystagmus	Yes	ND	Yes	ND
Gaze-evoked horizontal nystagmus	Yes	ND	Yes	ND
Oculomotor disorders	No	ND	ND	No
Diplopia or visual blurring	No	ND	ND	No
SARA score	0	ND	24	1.5
Noncerebellar symptoms, no/no total (%)				
Pyramidal syndrome	No	ND	No	No
Spasticity	No	ND	No	No
Motor impairment	No	ND	No	No
Sensory impairment	No	ND	ND	No
Hypopallesthesia	No	ND	ND	ND

Continued

Table 1 Characteristics of the Patients (in This Report) *(continued)*

Characteristics	Index case	Grandmother	Mother	Sister
Autonomic dysfunction				
Orthostatic hypotension	No	ND	ND	ND
Genitourinary dysfunction	No	ND	ND	No
Vestibular areflexia	No	ND	ND	ND
Sensory/motor axonal neuropathy	No	ND	ND	ND
Cognitive impairment	No	ND	No	No
Brain fog	Yes	ND	Yes	Yes
Brain MR				
Cerebellar atrophy on MRI	Yes	ND	ND	ND
Cerebellar vermian atrophy	Yes	ND	ND	ND
Cerebellar hemispheric atrophy	No	ND	ND	ND
Cortical atrophy	No	ND	ND	ND
Improvement with treatment				
Acetazolamide	Yes	ND	ND	ND
4-Aminopyridine	ND	ND	ND	ND

Abbreviations: ND = not determined, SARA = Scale for Assessment and Rating of Ataxia.

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Appendix *(continued)*

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