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Tremor and Other Hyperkinetic Movements

Reviews

Spinocerebellar Ataxia 27: A Review and Characterization of an Evolving Phenotype

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Abstract

Background: Spinocerebellar ataxia (SCA) is an uncommon form of progressive cerebellar ataxia with multiple genetic causes and marked variability in phenotypic expression even across patients with identical genetic abnormalities. SCA27 is a recently identified SCA caused by mutations in the Fibroblast Growth Factor 14 gene, with a phenotypic expression that is only beginning to be fully appreciated. We report here a case of a 70-year-old male who presented with slowly worsening tremor and gait instability that began in his early adulthood along with additional features of parkinsonism on examination. Work-up revealed a novel pathogenic mutation in the Fibroblast Growth Factor 14 gene, and symptoms improved with amantadine and levodopa. We also provide a review of the literature in order to better characterize the phenotypic expression of this uncommon condition.

Methods: Case report and review of the literature.

Results: Review of the literature revealed a total of 32 previously reported clinical cases of SCA27. Including our case, we found that early-onset tremor (12.1 ± 10.5 years) was present in 95.8%, while gait ataxia tended to present later in life (23.7 ± 16.7 years) and was accompanied by limb ataxia, dysarthria, and nystagmus. Other features of SCA27 that may distinguish it from other SCAs include the potential for episodic ataxia, accompanying psychiatric symptoms, and cognitive impairment.

Discussion: Testing for SCA27 should be considered in individuals with ataxia who report tremor as an initial or early symptom, as well as those with additional findings of episodic ataxia, neuropsychiatric symptoms, or parkinsonism.

Keywords: Ataxia, spinocerebellar ataxia 27, parkinsonism, tremor

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Introduction

Spinocerebellar ataxia (SCA) is a growing collection of autosomal dominant cerebellar ataxias for which the underlying genetic etiologies are being increasingly identified. To date, 44 SCA syndromes have been described, with the first genetic cause for SCA1 reported in 1994 and the most recent genetic cause for SCA44 reported in 2017.[1–3] As more causative genes are identified, marked variability in phenotypic expression has been noted across SCA syndromes and even within patients with the same genetic abnormality.[1,4] SCA27 was first reported in 2006, but the spectrum of phenotypic expression is only beginning to be elucidated.[5–17] We present here a patient who was found to have a novel, pathogenic mutation in the Fibroblast Growth Factor 14 (FGF14) gene located at chromosome 13q33, the gene associated with SCA27. We also provide a review of the literature in order to better characterize the phenotypic expression of this uncommon condition.

Case report

A 70-year-old male presented with worsening of a long-standing tremor as well as imbalance and gait instability. The tremor began roughly 50 years earlier in his 20s, was at first only noted in his right arm, and progressively worsened over the years, becoming more bothersome in the last couple of years. The tremor occurred at rest, with posture holding, and action, and persisted throughout the day.

Table 1. **Results of Search for Articles from PubMed Using Various Key Words and their Combinations**

Key Words and Combinations	Number of Publications		
	Total	Included	Excluded
FGF14	73	11	62 (not relevant)
Fibroblast Growth Factor 14	99	10	89 (not relevant)
SCA27	19	6	13 (not relevant)
Spinocerebellar ataxia 27	9	6	3 (not relevant)
FGF14 AND spinocerebellar ataxia	26	11	15 (not relevant)
Total number of articles identified from key word searches			226
Total number of additional articles included from the reference sections of the shortlisted articles			0
Final number of articles included for review after removing the duplicates			13

A mild tremor had developed in his left arm and head at some uncertain time in the past. He had been tried on propranolol and ropinirole for the tremor without benefit. The patient also reported difficulty with balance and walking a straight line, dating back potentially to elementary school. His balance and walking had been slowly worsening since childhood to the point that he had been falling two or three times a month for the last couple of years. He complained of diplopia and visual symptoms that had been present since adolescence and worsening for the last 7–8 years. Past medical history included psychiatric diagnoses including post-traumatic stress disorder and depression. He had completed vocational school after high school and had no current complaints of cognitive difficulties. The patient does not drink alcohol and therefore it is not known if the tremor is responsive to alcohol. Family history was notable for a father and paternal uncle with similar hand tremors, and a paternal aunt with a reported diagnosis of Parkinson's disease.

On examination, the patient had upbeating nystagmus with upward gaze as well as a persistent horizontal nystagmus with lateral gaze. He had mild symmetric rigidity in his bilateral upper extremities that increased with contralateral motor activation, along with mild bradykinesia and decrementing amplitudes with right-sided rapid finger tapping. Bilateral rest, postural, and intention tremors were observed in the bilateral upper extremities, right worse than left, along with a high frequency, low amplitude persistent head tremor. There was no tremor noted in the legs. Reflexes were normal and symmetric in the bilateral upper and lower extremities. Sensation was intact to light touch, vibration, and proprioception in the bilateral lower extremities. He had mild dysmetria on finger-follow and finger-to-nose testing bilaterally, as well as an ataxic, wide based gait.

Initial serological work-up was negative. Magnetic resonance imaging (MRI) of the brain was normal and without any evidence of cerebellar atrophy, findings suggestive of underlying multiple systems atrophy, or other degenerative cerebellar disorder. Given the nystagmus and progressive ataxia, genetic testing for SCAs was pursued and a missense mutation in the FGF14 gene (c.326T>C; p.Phe109Ser) was identified. This mutation had not been previously reported in a database search of dbSNP or 1,000 Genomes, and was predicted to be pathogenic, though verification of segregation of symptoms in his other reported family members was not possible as they are deceased.

The patient was started on amantadine, which improved his head tremor and led to marked improvement in falls with reduced gait instability. Three months later, he was started on one tablet of carbidopa/levodopa 25/100 mg three times a day, which further improved his hand tremor (rest more than postural and action) and gait instability. At follow-up 18 months from initial presentation, the patient has remained on the same doses of medication and continues to report improvement in his head tremor and balance. He does note that the tremor (rest, action, and postural) has worsened over time, but he denies any motor fluctuations related to the medications or dyskinesias and examination did not show any progression of other signs of parkinsonism.

Methods

Written consent was obtained from our case patient and we also subsequently performed a literature review to identify all manuscripts that provided clinical information on patients with a diagnosis of SCA27 due to genetic alterations of the FGF14 gene. We performed the search using PubMed in October 2017 including all dates of publication with the search terms of FGF14, Fibroblast Growth Factor 14, SCA27, Spinocerebellar Ataxia 27, and FGF14 AND Spinocerebellar Ataxia. A total of 226 papers were identified of which only 13 papers were found to contain positive patient information related to the diagnosis of SCA27 after exclusion of duplications. Details can be found in Table 1.

From these papers, a total of 38 individuals were identified by genetic testing, clinical examination, or family report of similar symptoms to gene-positive relatives.[5–17] Of the 38 patients reported, seven either did not have genetic confirmation of SCA27 or lacked any clinical examination information. One of these patients, however, was the father of two genetically confirmed, non-identical sons. Given the high likelihood

of the patient also having a gene mutation, his clinical data were included. Ultimately, six patients were excluded. Table 2 summarizes the demographic and clinical findings for the resulting 33 patients, including our case report, in which clinical and/or genetic data were usable.

Discussion

SCA27 is a slowly progressive, autosomal dominant cerebellar ataxia caused by a mutation in the FGF14 gene. The 14 initially reported patients, who are commonly referred to as the Dutch cohort, presented with a slowly progressive ataxia with postural tremor, and sometimes associated head titubation, as the initial manifestations.[5,6] In addition, these patients frequently had associated nystagmus, dysarthria, ambulation difficulties, limb ataxia, orofacial dyskinesias, psychiatric symptoms (depression and aggressive outbursts), and cognitive delay. However, since this initial description, an additional 19 patients, including our case, have been reported leading to expansion of the phenotype to include episodic ataxia and parkinsonism.[5–17] With the increased clinical information from the descriptions of 33 patients with SCA27 reported to date, we are better able to characterize the frequency of symptoms associated with this SCA and potentially improve our understanding of these symptoms.

Based on a recent review of the clinical features of 30 different autosomal dominant SCAs, SCA27 shares several cardinal features with these SCAs including ataxic gait (89.7% vs. 97%), nystagmus (84% vs. 56%), dysarthria (91.3% vs. 90%), and limb ataxia (81.8% vs. 94%).[4–16] Tremor was found to be present in a much higher percentage of SCA27 patients (95.8%) than observed on average among other SCAs (40%).[4–8,11–16] The percentage of those SCA27 patients with tremor was also higher than the other SCAs most commonly associated with tremor including SCA2 (49.8%) and SCA12 (70%).[4] Tremor was also the initial presenting symptom in 57.7% of SCA27 patients compared with an average of 4% seen among other SCAs.[4–17] Initial symptom onset occurs earlier in life in SCA27 than other SCAs (12 $\pm$ 10 years vs. 35 $\pm$ 11 years), yet it appears to have a slower progression than other SCAs with only 13.8% of patients reporting severe gait impairment and only 17.4% reporting severe dysarthria despite having symptoms for several decades.[1,4–17] This finding is frequently seen among the non-polyglutamine expansion SCAs, even when only comparatively followed for a few years.[17,18] Finally, 20% (four out of 20) of the SCA27 patients with MRI information were reported to have abnormal MRI with evidence of cerebellar atrophy.[5–16] Comparatively, during the disease course of other SCAs, cerebellar hemisphere or vermian atrophy is frequently reported in addition to more disease-specific findings of brainstem, pontine, basal ganglia, or cortical atrophy.[1,19]

Like other reported types of SCAs, SCA27 has been associated with the occurrence of non-ataxia symptoms. For example, psychiatric symptoms including depression and aggressive outbursts were reported in 56% of patients.[5–17] This suggests a higher incidence rate than reported in other SCAs with the exception of SCA2, SCA17, and dentatorubro-pallidoluysian atrophy, which have occurrence rates as high as 87%, 63%, and 65%, respectively.[4] Cognitive impairment may also be a more prominent feature in SCA27 as it has been reported in 50% of patients, whereas across other autosomal dominant SCAs it has only been reported in about 20% of patients.[4–17]

Episodic ataxia, reported in 21.2% of SCA27 patients, is another feature that is uncommon among most SCAs.[5–17,20,21] SCA6, which is caused by mutations in the CACNA1A gene, is the only other SCA infrequently associated with an episodic ataxia, though mutations in this gene also cause episodic ataxia 2.[20,22] The FGF14 gene, like the genes linked to SCA6 and the autosomal dominant episodic ataxia disorders, has been associated with ion channels and excitatory neurotransmission, potentially explaining the development of episodic ataxia in some of these patients.[20,22–26]

The addition of our patient case presented here potentially expands the phenotypic expression of SCA27 to include a dopamine-responsive parkinsonism (bradykinesia, rigidity, and rest tremor). FGF14 is trafficked to and expressed in axons of the striatopallidal and striatonigral pathways, and FGF14 knockout mice have been shown to have an inappropriate response to dopaminergic stimulation[27] that could potentially contribute to the development of parkinsonism in some SCA27 patients. Limited information could be gleaned from our literature search about the presence of parkinsonian features in prior SCA27 reports. Several of the patients from the Dutch cohort were trialed on a "dopaminergic medication" with no reported improvement in tremor.[5,6] One subject in the Dutch cohort even underwent dopamine imaging as part of his work-up with the findings reported to be not consistent with a diagnosis of Parkinson's disease.[5,6] Dyskinesias have also been reported in 10 prior cases of SCA27, but details are lacking to determine what these movements represent and if there was any relation to dopaminergic therapy or not.[5,6] Overall, our case in combination with prior SCA27 reports support that some patients may manifest parkinsonian symptoms.

Our patient also showed improvement in head tremor and gait stability when started on amantadine. Amantadine slows the inactivation of sodium channels and thus may allow for increased excitation, helping to reverse the decreased cell firing of Purkinje and granule cells after depolarization that is associated with the genetic defect in FGF14.[28–30] Although amantadine has previously been shown to potentially help improve cerebellar ataxia, Friedreich's ataxia, and parkinsonism,[31,32] there are no reports to date of amantadine or any other medication found to successfully reduce tremor and/or gait stability in SCA27.[5–17] Thus, research is needed to better determine if amantadine or levodopa may be reasonable treatment options to consider for SCA27.

There are some limitations to this review including the overall small number of SCA27 cases reported to date and the inconsistent reporting of clinical features, particularly related to parkinsonism, cognition, and particularly mood with the initial Dutch cohort entailing the majority of patients with neuropsychiatric complaints. Additionally, apart from the initially identified mutation in the FGF14 gene (F145S), the pathogenicity of each reported genetic alteration has not been verified with in vitro or animal model testing to prove causality and thus remains an area in need of further research. While SCA27 may be

Table 2. **Patient Demographics and Clinical Information for all Reports to Date**

Reference	Gender	Age[1] (years)	Ataxia Onset (years)	Tremor Onset (years)	Ataxia			Nystagmus	Dysarthria	Tremor	Dyskinesia	Parkinsonism	Psychiatric Symptoms	Education Level
					Limb	Gait	Episodic							
Van Swieten (2003); Brusse (2006)	M	79	30	10	++	+++	NR	+	+++	+	+	NR	AO	PS
	M	71	36	10	++	+++	NR	–	+++	+	–	NR	D	<PS
	M	69	27	20	++	++	NR	+	++	+	+	NR	–	PS[2]
	F	64	50	10	+	++	NR	–	++	+	+	NR	–	SE[2]
	M	61	30	10	+	+	NR	+	++	+	+	NR	–	<PS
	F	54	40	12	+	+	NR	+	++	+	+	NR	–	SS
	F	31	37	8	+	+	NR	+	+	+	+	NR	AO	PS
	F	30	30	20	+	–	NR	+	+	+	–	NR	AO	SE
	M	27	–	10	–	–	NR	+	+	+	+	NR	AO	PS
	F	48	30	10	+	+	NR	+	+	+	–	NR	–	SS[2]
	M	42	35	10	–	+	NR	+	+	+	–	NR	–	PS
	F	43	40	12	–	+	NR	+	+	+	+	NR	–	SS
	M	39	–	6	–	+	NR	+	–	+	–	NR	AO	SE
	F	24	18	7	+	–	NR	+	–	+	–	NR	D	SS
Dalski (2005)	M	13	12	12	NR	+	NR	+	NR	+	NR	NR	D	NR[2]
Misceo (2009)	F	5.5	1	2.5	NR	++	NR	–	+	+	+	NR	NR	SE[2]
	F	42	NR	NR	NR	+	NR	NR	NR	NR	NR	NR	NR	SE[2]
Shimojima (2012)	M	3.75	NR	NR	NR	NR	P	NR	NR	NR	+	NR	NR	SE[2]
Chen (2012)	M	61	38	NR	++	+++	NR	+	+++	NR	NR	NR	NR	NR
	M	NR	50	NR	++	+++	NR	+	+++	NR	NR	NR	NR	NR
	M	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Coebergh (2013)	M	2	2	–	+	+	P	++	+	–	–	NR	NR	NR
	F	36	NR	NR	NR	+	NR	+	NR	NR	NR	NR	NR	NR
	F	66	NR	49	NR	+	NR	NR	NR	+	NR	NR	NR	NR
Tucker (2013)	M	4.5	1	1	NR	+	NR	NR	NR	+	NR	NR	NR	SE[2]
Choquet (2015)	M	31	26	29	+	+	P	+	+	+	NR	NR	NR	NR
	M	NR	NR	NR	NR	+	P	+	+	NR	NR	NR	NR	NR
	F	NR	NR	NR	NR	NR	P	+	NR	NR	NR	NR	NR	NR
	M	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Planes (2015)	F	20	1	1	+	++	NR	–	NR	+	NR	NR	NR	SE[2]
Amado (2017); Blanco-Barca (2017)	F	4	1.5	4	+	+	P	+	+	+	NR	NR	NR	SE[2]
	F	4.5	1.5	4	+	+	P	+	+	+	NR	NR	NR	SE[2]
Present Case	M	70	8	20	++	+	–	++	+	++	–	+	D	SS
Totals	18 M/15 F	37.3 ± 24.4	23.7 ± 16.7	12.1 ± 10.5	81.8% (18/22)	89.7% (26/29)	21.2% (7/33)	84% (21/25)	91.3% (21/23)	95.8% (23/24)	55.6% (10/18)	100% (1/1)	D – 25% (4/16); AO – 31.3% (5/16)	SE – 45.5% (10/22); 2 – 50% (11/22)

Abbreviations: –, Not Present; +, Mild; ++, Moderate; +++, Severe; AO, Aggressive Outbursts; D, Depression; F, Female; M, Male. NR, Not Reported; P, Present; PS, Primary School; SE, Special Education; SS, Secondary School.

[1]Age at time of examination/reporting and not necessarily age at diagnosis.

[2]Evidence of cognitive impairment.

a rare disease, it is also possible that the diagnosis is being missed or that patients are being incorrectly diagnosed with essential tremor (ET) due to the early onset of tremor, its slow progression, and the attribution of gait ataxia to the "cerebellar signs" of ET.[33] In our patient case, it is possible some of the motor symptoms are due to concurrent Parkinson's disease and SCA27. We do not have dopaminergic imaging, though the utility of such imaging in SCA27 is questionable given that several SCAs with associated parkinsonism, including SCA2, SCA3, and SCA17, can have abnormal dopaminergic imaging.[34–37] Therefore, such imaging is unlikely to be able to confirm the diagnosis of Parkinson's disease. Our patient also has not shown progression of his parkinsonism over the last 18 months, which helps support that his findings are not related to underlying Parkinson's disease. However, post-mortem examination would provide the best clarification as to whether pathology that represents typical Parkinson's disease exists or not.

In summary, this study provides a synopsis of the clinical characteristics of SCA27 based on gene-confirmed cases reported to date. Our findings support that tremor is an early and prominent feature in SCA27, and that the disorder may be associated with episodic ataxias as well as non-ataxia features including psychiatric symptoms and cognitive impairment. We also report parkinsonism as a potential feature of SCA27, though further follow-up and research will be needed to fully determine its possible association. Marked overlap in the phenotypic expression of the multiple SCAs can lead to difficulties with predicting which SCA the patient is likely to have prior to genetic testing.[1] Therefore, consideration for SCA27 should be high for individuals with ataxia and tremor as initial, or early, symptoms as well as those with psychiatric symptoms, cognitive delay, parkinsonism, or episodic ataxia. Finally, if SCA27 is diagnosed, a trial of amantadine could be considered.

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