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### Pearls & Oy-sters: ATX-FGF14 Mimicking Autoimmune Pathology

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## **Abstract**

ATX-FGF14 (formerly spinocerebellar ataxia 27, OMIM #193003) is an autosomal dominant condition caused by a pathogenic variant in the fibroblast growth factor 14 (*FGF14*, OMIM #601515) gene located on chromosome 13. The phenotypic expression can vary in patients with the same genotype, often delaying diagnosis, especially in probands without known affected relatives and/or with limited available family history. We describe two cases of ATX-FGF14 in one family with a focus on the importance of differentiating episodic manifestations of neurogenetic conditions from inflammatory/autoimmune neurologic conditions. A 68-year-old male patient (Case 1) presented with episodic dysarthria, dizziness, imbalance, and encephalopathy, creating suspicion for a possible autoimmune etiology. At first evaluation, the patient reported no significant family history. Four years later, upon revisiting the family history, he noted that his 49-year-old niece (Case 2) had also developed neurologic symptoms of an unclear etiology. On evaluation, she had tremor and ataxia. Both patients also had coexistent evidence of systemic autoimmunity that likely contributed to the initial suspicion of neurologic autoimmunity, and neither had cerebellar or brainstem volume loss. Ultimately, their genetic testing revealed a pathogenic structural variant in the *FGF14* gene, consistent with ATX-FGF14. These two cases highlight the importance of a detailed interval family history at each visit, especially in undiagnosed adult patients, as well as the importance of objectively analyzing the impact of immunotherapy diagnostic treatment trials to avoid unnecessary immunomodulatory medications.

## Pearls

- Clinicians should request an updated interval family history at each visit, especially in undiagnosed adult patients.
- Slowly progressive cerebellar ataxia and episodic cerebellar features can be observed in the *FGF14* gene pathogenic variant. Only 20% of patients with ATX-FGF14 show MRI-based cerebellar volume loss.

## Oy-sters

- Late-onset genetic disorders can be easily misdiagnosed as inflammatory/autoimmune neurologic conditions.
- Non-specific serologic abnormalities can be observed in healthy individuals. Physicians should be aware of the limitations of tests directed at screening for systemic autoimmunity.

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## Case reports

### Case 1

A 68-year-old man was referred to the autoimmune neurology clinic for evaluation of 8 months of episodic dysarthria, dizziness, and imbalance. Episodes occurred every other day, with each episode lasting 30 minutes. He had no preceding febrile illness or reported stressors. The symptoms progressed, and at the time of consultation, the patient experienced several attacks daily, each lasting a few hours. He also reported 10 years of progressive difficulty writing with his dominant left hand. Neurological examination revealed mild dysarthria, downbeat nystagmus, esotropia, and dysmetria. Strength, sensation, and reflexes were normal. Serologic testing 8 months prior to the referral showed elevated anti-double stranded DNA antibody (236 IU/ml; normal range: <100 IU/ml), anti-thyroid peroxidase (TPO) antibody (84.3 IU/ml, normal range 0-4 IU/ml), and thyroglobulin antibody levels (4.6 IU/ml, normal range 0-3.9 IU/ml). The patient had no symptoms of thyroid disease. Other laboratory screening was unremarkable, including thyroid-stimulating hormone, autoimmune (Sjogren's syndrome [SS] A and SSB antibody), infectious (HIV, varicella-zoster virus [VZV], herpes simplex virus [HSV], rapid plasma reagin), metabolic/toxic (copper, vitamin B1, vitamin B12, vitamin E), and paraneoplastic evaluation (NMDA receptor, leucine-rich glioma inactivated 1, amphiphysin, contactin-associated protein-like 2, CV2/collapsin response mediator protein 5, Hu, Ri, Yo, Ma1, Ma-2/Ta, Zic4, and glutamic acid decarboxylase 65 antibody in both serum and CSF). CSF analysis showed normal cell count, protein, glucose, and immunoglobulin (Ig) G index. CSF oligoclonal band (OCB) analysis detected two unique IgG bands. Routine EEG and contrast MRI of the brain were normal. Whole-body PET/ CT scan was normal. He was treated empirically for an autoimmune neurological condition with high-dose intravenous methylprednisolone therapy for three days,

followed by prednisone 60 mg, which was slowly tapered to 15 mg at the time of referral. He had also received intravenous immunoglobulin (IVIg) therapy for 2 g/kg over five days, two months before the referral. During the IVIg, he developed venous thromboembolism and was started on warfarin. No substantial improvement was observed with immunotherapies. At the time of consultation, the patient reported no significant family history.

Additional laboratory evaluation after the referral revealed antinuclear antibody titer of 1:40 (both speckled and nucleolar patterns) and elevated beta-2 glycoprotein-1 (B2GP1) IgM of 24 (normal range: 0–20 SMU) and anti-cardiolipin IgM of 17 (normal range: 0–12 MPL). B2GP1 IgG, anti-cardiolipin IgG, and lupus anticoagulant were negative. Repeat MRI demonstrated mild but age-appropriate cerebellar volume loss (Figure 1A,B). A diagnosis of antiphospholipid syndrome (APS) was considered but the repeat APS work-up after 12 weeks was negative. At follow-up, his episodic symptoms continued to increase in duration, lasting 30 minutes to 6 hours. The spells improved in both duration and frequency on acetazolamide. Three years later, he also noted weakness and shaking in his legs during these events. Four years after the first clinic visit, while revisiting family history, the patient noted that his niece (Case 2) had recently developed neurologic symptoms.

## **Case 2**

A 49-year-old woman with a history of insulin-dependent diabetes and hypothyroidism presented to the autoimmune neurology clinic for evaluation of progressive ataxia and tremor. The patient reported 3 years of action tremors and word-finding difficulties. MRI of the brain obtained at that time was unremarkable (Figure 1C, D). Six months after symptom onset, she started experiencing episodes of body shaking lasting for minutes without loss of consciousness or confusion. She subsequently developed progressive gait instability, vertigo, and oscillopsia.

Neurological examination revealed down beat nystagmus, esotropia, hypermetric saccades, dysmetria in the bilateral upper extremities, impaired rapid alternating movements, and a wide base gait. Strength, sensation, and reflexes were intact.

Work-up at the time of symptoms onset was negative for infectious, metabolic/toxic, and autoimmune etiology, except for elevated anti-TPO antibody at 226.3 IU/ml. CSF analysis showed pleocytosis of 164 (99% lymphocytes). CSF glucose, protein, IgG index, and OCB were unremarkable. CSF cryptococcus antigen, VZV, HSV, and Leukemia/lymphoma phenotyping were negative. Autoimmune/paraneoplastic encephalopathy-associated antibodies in CSF were negative, similar to Case 1. Whole-body CT was unremarkable. Thirty months before her visit, the patient was diagnosed with presumed seronegative autoimmune encephalitis and was initiated on 40 mg of prednisone, which was titrated off after 6 weeks. She was also started on rituximab 24 months before consultation (1 g IV on day 1, day 14, 6 months, and 1 year). One year before the visit, she was initiated on IVIg 0.4 g/kg every 4 weeks. She demonstrated no improvement with immunotherapies. She also started acetazolamide twice a day, which helped with spells of body shaking. On initial evaluation at the autoimmune neurology clinic, she was not on immunotherapy.

Upon detailed questioning, the patient reported that her father, who died at 74 years of age due to prostate cancer, had chronic ataxia and dysarthria, and that her paternal grandmother frequently fell owing to imbalance. Repeat CSF analysis was unremarkable. Given the now substantial family history of neurological symptoms, genetic counseling and subsequent genetic testing was undertaken. Whole genome sequencing with genome-wide structural variant analysis at *Variantyx*<sup>1</sup> revealed a heterozygous 235.50-kb deletion in the 13q33.1 region intersecting the fibroblast growth factor 14 (*FGF14*) gene (GRCh38/hg38 13q33.1 chr13:101776915-

102012410x1). The patient was diagnosed with ATX-FGF14. Her paternal uncle's (Case 1) genetic testing was performed at Invitae<sup>2</sup>, where *FGF14* sequencing and deletion/duplication analysis also revealed deletion of *FGF14* exon 1-3. While this sequencing was unable to determine the breakpoints of this deletion, both identified deletions encompassed exons 1-3 of the *FGF14* gene. A pedigree chart (Figure 2) shows dysarthria, nystagmus, tremor, gait instability, and cognitive disorder across generations, suggesting a neurogenetic etiology.

## Discussion

The *FGF14* gene encodes fibroblast growth factor-14, which is highly expressed in Purkinje cells that regulate neuronal excitability.<sup>3,4</sup> *FGF14* pathogenic variants have been associated with ATX-FGF14, an autosomal dominant condition formerly known as spinocerebellar ataxia (SCA) 27, characterized by cerebellar dysfunction resulting in gait disturbances, ataxia, tremors, dysarthria, and gaze-evoked nystagmus.<sup>5</sup> Symptoms can be exacerbated by fever or stress.<sup>4</sup> In Case 2, the CSF pleocytosis may have been indicative of a viral or inflammatory trigger, as CSF pleocytosis has not previously been associated with ATX-FGF14. Episodic ataxia may distinguish *FGF14* pathogenic variants, including ATX-FGF14, from other SCAs.<sup>4,5</sup> The pathogenic variant observed in Case 2 (GRCh38/hg38 13q33.1 chr:101776915-102012410x-1) has not been previously reported. The highly variable age of onset and slow progression of ATX-FGF14 may delay diagnosis, particularly without a known family history or in late-onset cases. Intronic GAA repeat expansion in the *FGF14* gene has been related to late-onset cerebellar ataxia, emphasizing the importance of considering an expansion repeat disorder, particularly with symptoms of onset after the sixth decade of life, positive family history, and episodic ataxia at onset.<sup>3,6</sup>



A retrospective study of 20 patients with ATX-FGF14 found that only 20% were described as having cerebellar volume loss on MRI.<sup>7</sup> The patients in our study had age-appropriate cerebellar and brainstem volumes and did not demonstrate significant signal abnormalities within the pons such as “hot crossed buns sign” or vertical pons hyperintensity which have been described for other subtypes of SCA, such as SCA2.<sup>8</sup>

Both patients showed evidence of systemic autoimmunity leading to the consideration of immune-mediated cerebellar ataxias (IMCA) (e.g. paraneoplastic cerebellar degeneration, post-infectious cerebellitis, and other neuronal antibody-mediated conditions). IMCA is typically acute or subacute, whereas genetic ataxias tend to progress slowly over many years.<sup>9</sup> IMCA has rarely been associated with a family history of ataxia.<sup>9</sup> Further, neuronal autoantibodies and cancer evaluation were negative in both patients, and neither patient met the diagnostic criteria for autoantibody-negative autoimmune encephalitis.<sup>10</sup> We have no evidence that the patients’ systemic autoimmunity is related to their pathogenic variant. Retrospectively, in both cases, the first-line study results for ataxia, including thyroid function, metabolic/toxic, autoimmune, infectious, and malignancy workup, were unrevealing, and genetic testing (even without a family history) should be considered, given how common genetic factors are in the etiology of progressive ataxia.<sup>11</sup>

Both patients in this study showed some improvement in their episodic symptoms after the initiation of acetazolamide, which could be a clue to diagnosis. Historically, acetazolamide has been used in episodic ataxia. An open clinical trial involving nine patients with SCA6 demonstrated that acetazolamide temporally alleviated the severity of cerebellar ataxia. Acetazolamide may improve episodic ataxia in individuals with ATX-FGF14; studies are required to corroborate this finding.

In conclusion, a willingness to abandon presumptive autoimmune diagnoses not responding to empiric immunotherapy and not clearly fitting the phenotype is essential to avoid unnecessary medication exposures and to end prolonged diagnostic odysseys. It remains paramount to query updated family history and to frequently revisit presumptive diagnoses in the long-term follow-up.

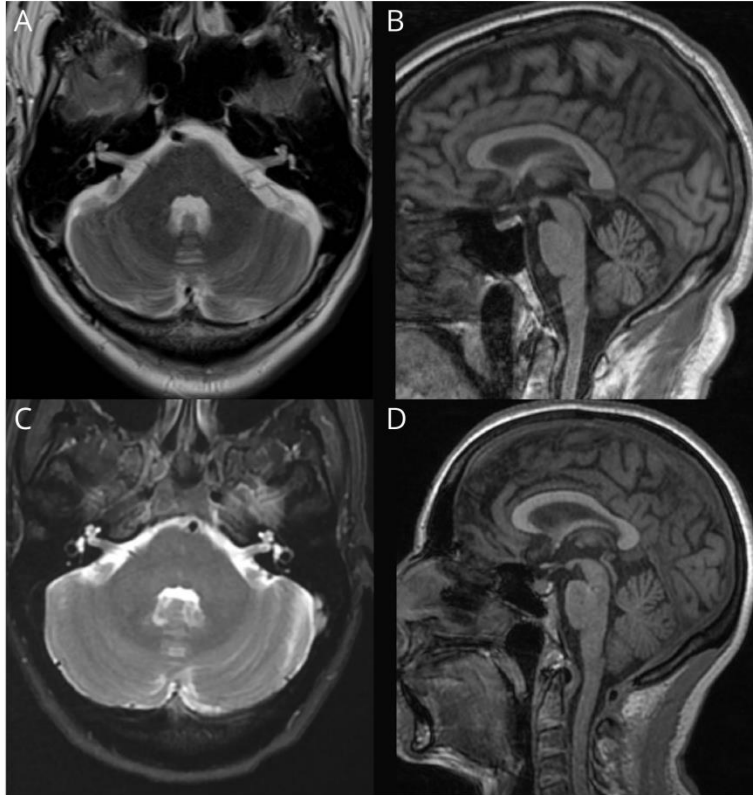
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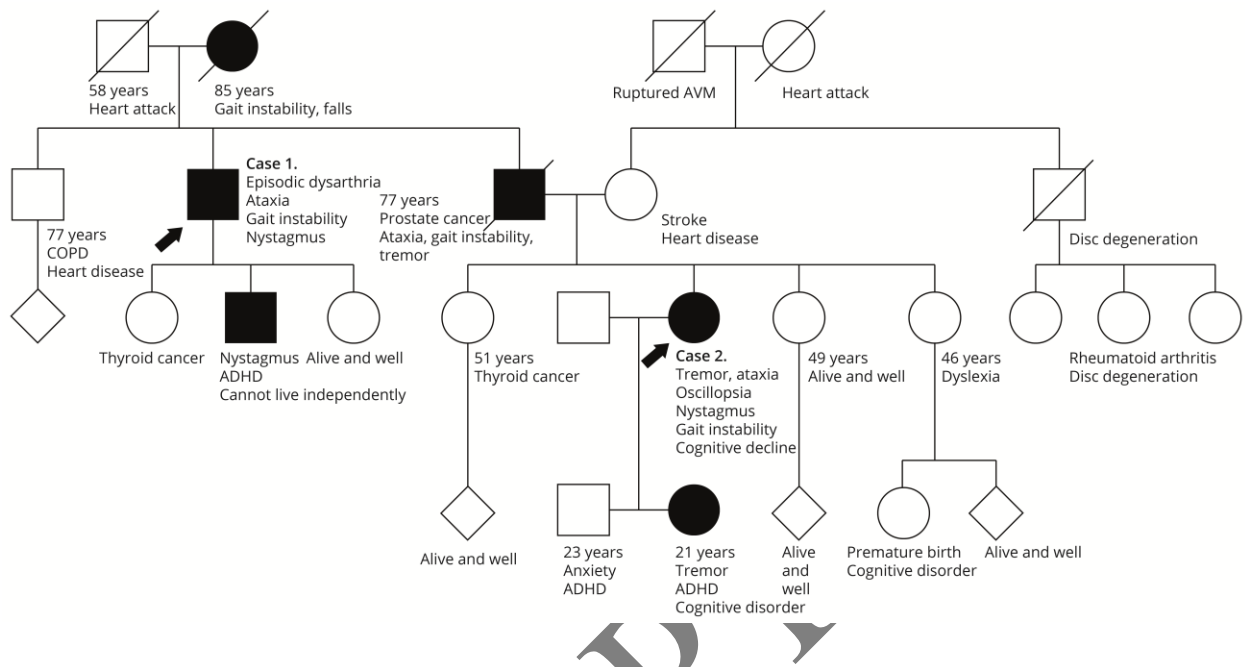
**Figure legends:**

**Figure 1.** MRI of the brain for Cases 1 (A, B) and 2 (C, D)



Axial T2-weighted (A) and sagittal Magnetization Prepared-Rapid Gradient Echo (B) images demonstrate mild cerebellar hemispheric and vermian atrophy in Case 1. The degree of atrophy was within one standard deviation of the mean for age on quantitative analysis. Axial T2-weighted fat-saturated (C) and sagittal MRI 3D brain volume T1-weighted (D) images demonstrate normal cerebellar and brainstem volumes without signal abnormality in Case 2. Quantitative analysis was performed using NeuroQuant software (CorTechs Labs, San Diego, California).

**Figure 2.** Four generation Pedigree chart



Six family members exhibited neurological symptoms. Case 1 and 2 are indicated by arrows.

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