Clinical Reasoning: A 13-year-old boy with chronic ataxia and developmental delay

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SECTION 1

A 13-year-old boy presented to the neurology clinic for evaluation of ataxia and intellectual disability. He was born at term via vaginal delivery after an uncomplicated pregnancy with no perinatal complications. Newborn screening (Virginia, 2012) was normal. He was first noted to be ataxic at age 6 months (when he began to sit with support) and his symptoms gradually worsened over time. He had global developmental delay. He began to sit at 14 months of age and walked at 20 months. He had his first words around age 2 and received physical and speech therapy early on. He had acute worsening of his symptoms at age 8 months in the setting of a flu-like illness and was admitted to a local hospital. Workup at the time was reportedly unrevealing and included a normal CT and a normal brain MRI with contrast. His ataxia remained fairly stable over time without regression. He had several episodes of

acute worsening with febrile illnesses. He continued to have learning problems at school.

His general examination at the time of initial clinic visit was unremarkable. On neurologic examination, he was alert and cooperative. He had dysarthria. He had normal tone and strength with exaggerated muscle stretch reflexes, most notable in the legs. He was observed to have choreoathetoid movements of the face, arms, and legs. He had bilateral dysmetria and dysdiadochokinesia. His gait was unsteady and wide-based.

Questions for consideration:

1. What category of ataxia would you consider in this case?
2. What additional historic details would be important to obtain?

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SECTION 2

The patient's presentation is consistent with cerebellar ataxia. Cerebellar ataxias are usually classified based on the duration of symptoms into acute (days), subacute (months), and chronic (years).¹ The most common causes for acute ataxias are toxic (e.g., alcohol ingestion), vascular (e.g., cerebellar hemorrhage or stroke), and infectious etiologies (e.g., varicella). Subacute ataxia usually results from posterior fossa tumors, nutritional deficiencies (e.g., vitamin B12, vitamin E, copper and folate), or autoimmune disorders (e.g., antiglutamic acid decarboxylase). Our patient has chronic ataxia, for which the 2 main categories to consider are hereditary disorders (e.g., spinocerebellar ataxias [SCAs]) and ataxias caused by inborn errors of metabolism (e.g., Refsum disease). Brain MRI, preferably with contrast, is helpful in patients with ataxia.² It may show abnormalities in the cerebellum, with or without associated abnormalities in the supratentorial and infratentorial structures, the brainstem (e.g., congenital disorders of glycosylation), or the spinal cord (e.g., Friedreich ataxia). Imaging characteristics can help to narrow the differential diagnosis; for example, contrast enhancement may indicate inflammatory or infective etiologies. Serial imaging is helpful in monitoring changes and detecting new abnormalities. Serial normal imaging could be more suggestive of a genetic disorder such as Rett syndrome.²

Our patient had a repeat MRI at age 12 that remained unremarkable.

A detailed family history is critical when considering a genetic disorder. Further history obtained for this child revealed that the patient's mother also had ataxia. She initially developed ataxia at age 3 during a febrile illness then had full recovery. The ataxia recurred at age 20 when she was pregnant with her second child (the patient); her symptoms had been slowly progressive since then. She eventually became wheelchair-bound. She was evaluated in the adult neurology clinic, where her examination showed severe truncal and appendicular ataxia, spastic dysarthria, and bilateral dysmetria.

The mother had previously undergone an extensive evaluation including MRI/magnetic resonance angiography of the brain, EMG/nerve conduction studies, muscle biopsy, antineuronal antibody testing, antigliadin and transglutaminase immunoglobulin A and immunoglobulin G, thyroid antibodies, and *CACNA1A* mutation testing for familial hemiplegic migraine. She had an ataxia panel testing for SCAs and episodic ataxia syndromes including SCA1, 2, 3, 6, 7, 8, 10, and 17; dentatorubral-pallidoluysian atrophy; Friedreich ataxia; complete sequence analysis of *APTX* (for ataxia with oculomotor apraxia [AOA]1); *SETX* (for AOA2); *PRKCG* (for SCA14); *SIL1* (for Marinesco-Sjögren syndrome); *TTPA* (for ataxia with vitamin E deficiency); select exon analysis of *POLG1*

Figure Family pedigree of the patient shows different neurologic presentation in different family members

Wt = wild-type.

(for 2 mitochondrial recessive ataxia syndrome mutations); *SPBN2* (for 3 known SCA5 mutations); and *KCNC3* (for 2 known SCA13 mutations). All were unrevealing. The patient's 14-year-old brother was diagnosed with generalized epilepsy. He, however, did not have ataxia or developmental delay. Our patient had 2 maternal aunts who died in the first

decade of life and had epilepsy. See the pedigree for details (figure).

Questions for consideration:

1. What is your differential diagnosis?
2. What investigations would you order next?

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SECTION 3

Chronic ataxia with normal MRI raises concern for a genetic disorder, and the family history suggests an inherited syndrome. Based on the family pedigree, the presumed mode of inheritance is autosomal dominant; however, maternally inherited mitochondrial disorders should also be considered. The episodic nature of the symptoms suggests a paroxysmal disorder such as a channelopathy.³

Given continued concern for an inherited/genetic disorder, a chromosomal microarray was ordered for

our patient and was normal. Whole exome sequencing (WES) was subsequently ordered and showed an *ATP1A3* variant, *c.2267G>A, p.R756H* (*NM_152296*), which was maternally inherited. No other variants were noted.

Questions for consideration:

1. What is *ATP1A3*?
2. What are the phenotypes associated with this gene mutation?

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SECTION 4

The *ATPIA3* gene is located on chromosome 19q13.2 and encodes the $\alpha 3$ subunit of the Na⁺/K⁺ transporting ATPase. *ATPIA3* pathogenic variants have been previously associated with rapid-onset dystonia parkinsonism; alternating hemiplegia of childhood; and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss. More recently, it has been linked to early-onset epileptic encephalopathy and episodic prolonged apnea and to relapsing encephalopathy with cerebellar ataxia.⁴ All of these variable phenotypes associated with *ATPIA3* pathogenic variants can occur sporadically as a result of a de novo mutation or can be inherited. Inheritance is autosomal dominant.

The *c.2267G>A, p.R756H (NM_152296)* variant is located in exon 17 of *ATPIA3*. This alteration results from a G to A substitution at nucleotide position 2267, causing the arginine (A) at the amino acid position 756 to be replaced by a histidine (H). This amino acid change has been observed in affected individuals, including a father and his daughter with rapid-onset dystonia parkinsonism,⁵ and a 34-year-old woman with relapsing cerebellar ataxia, generalized dystonia, pyramidal signs, and anger outbursts.⁶ Nearby alterations have been reported in patients with alternating hemiplegia of childhood.⁷ The alteration cosegregated with disease in the family described here, as it is present in heterozygous form in the patient's mother but not in his father. The altered amino acid is conserved throughout evolution. The alteration is not observed in healthy individuals and is predicted to be deleterious by in silico models. The mutation was therefore determined to be likely pathogenic. The patient's brother was not found to have the same alteration. His epilepsy is likely related to a different etiology.

DISCUSSION This case demonstrates 2 genetic phenomena: variable expressivity and pleiotropy. Variable expressivity measures the extent to which a genotype exhibits its phenotypic expression. The patient and his mother both have ataxia but have differing degrees of severity.

Pleiotropy describes the varying phenotypic traits that can manifest from a single gene mutation.⁸ In this case, the same *ATPIA3* gene mutation manifests as ataxia, chorea, and athetosis in the patient and as ataxia in his mother.

There are multiple factors that can lead to pleiotropy and variable expressivity of a phenotype. Perhaps the least understood and most challenging factors to study include environmental and lifestyle factors. Modifier genes, on the other hand, are well-described effectors of phenotype in certain diseases. A modifier gene alters the expression of another gene by influencing transcription of the gene itself or phenotypes at the

cellular or organismal level. This can in turn lead to entirely distinct phenotypes as well as varying severity of disease.⁸ Modifier genes have been implicated in the phenotypic expression of many neurologic (and non-neurologic) diseases. For example, they are thought to affect severity of renal disease in tuberous sclerosis⁹ and café-au-lait macule count in neurofibromatosis type 1.¹⁰ The cause for the phenotypic variance in the case of *ATPIA3* has yet to be studied.

The complexity of genetic inheritance can make diagnosis of a genetic condition challenging, time-consuming, and invasive, as was the case for this patient and his family. WES is a tool that allows for clinicians and researchers alike to solve diagnostic mysteries. In some cases, such as this, WES can be the last available opportunity to provide the patient and family with an answer and arguably should be considered early in the diagnosis process. This testing method not only has allowed for discovery of new diseases but has also defined new phenotypes for a previously described genetic variant. This case provides one example of the many diagnostic odysseys that occur in genetics. Description of this family's phenotypic variants provides evidence to support evaluation for an *ATPIA3* gene mutation in the case of familial cerebellar ataxias.

AUTHOR CONTRIBUTIONS

Dr. Amal Abu Libdeh: chart review, drafting the manuscript, analysis and interpretation of data. Dr. Lauren Talman: chart review, drafting the manuscript, analysis and interpretation of data. Chelsea Chambers: acquisition of data, analysis and interpretation of data. Dr. Radhika Dhamija: acquisition of data, study supervision, and critical revision of the manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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