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Tremor and Other Hyperkinetic Movements

Case Reports

Progressive Ataxia with Elevated Alpha-Fetoprotein: Diagnostic Issues and Review of the Literature

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Abstract

Background: Ataxias represent a challenging group of disorders due to significant clinical overlap. Here, we present a patient with early-onset progressive ataxia, polyneuropathy and discuss how elevation of alpha fetoprotein (AFP) narrows the differential diagnosis.

Case report: Ataxia, polyneuropathy, and mild elevation of AFP are features compatible with ataxia with oculomotor apraxia type 2 (AOA2) but also with ataxia with oculomotor apraxia type 4 (AOA4). A genetic analysis demonstrated biallelic mutations in senataxin (*SETX*), confirming the diagnosis of AOA2.

Discussion: Mild elevation of AFP is found in patients with AOA2 and AOA4, and higher levels are commonly seen in ataxia-telangiectasia. AFP is a useful diagnostic tool but not a biomarker for disease progression in AOA2.

Keywords: Ataxia, alpha-fetoprotein, polyneuropathy, senataxin, cerebellar atrophy

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Supplementary material: To access the supplementary material, please visit the article landing page.

Introduction

Early-onset/juvenile ataxia is usually a challenging diagnosis due to significant clinical overlap. Here, we discuss the utility of alpha-fetoprotein (AFP) for the investigation of ataxia syndromes associated with polyneuropathy and hyperkinesias such as chorea and dystonia. First, we describe a patient featuring the clinical and laboratory signs of ataxia with oculomotor apraxia 2 (AOA2). We use this case as a platform to discuss diagnostic issues, review the literature, and the limitations of AFP as a biomarker for disease progression.

Case presentation

A Swedish 29-year-old woman, born to nonconsanguineous healthy parents, was referred to our center for evaluation. There was no family history of neurological disease. At age 5, the patient's parents noticed mild clumsiness but the patient was able to participate in sporting activities. However, marked worsening occurred during early puberty, affecting her balance, and both slurred speech and diplopia appeared at this point. From age 15, the patient was evaluated at other hospitals, and those investigations revealed axonal sensorimotor polyneuropathy and cerebellar

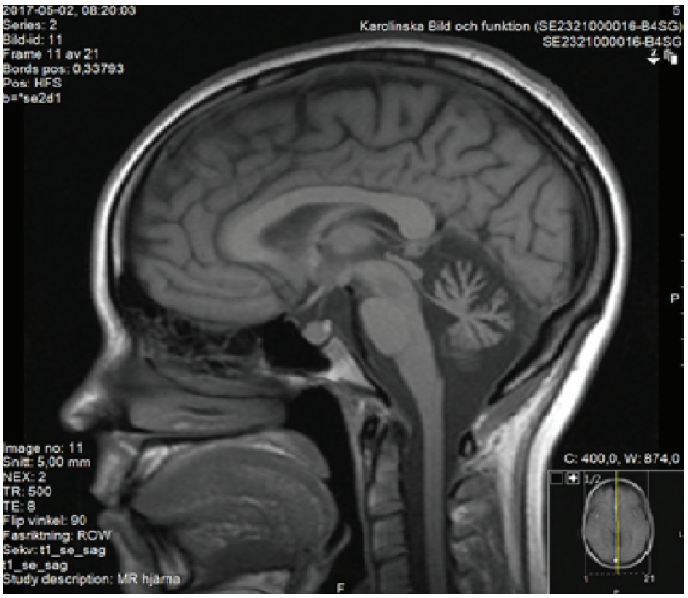

Figure 1. **Neuroimaging in AOA2.** Midsagittal T1-weigthed brain MRI of the patient at age 27 showing moderate cerebellar atrophy and enlarged interfolial spaces.

atrophy. However, no etiological diagnosis was established. Diplopia was caused by strabismus and was treated at age 21 with prism lenses and at 26 with surgery. However, these surgeries had transient benefit only. There was no indication of cognitive deficits, and the patient finished her training as a laboratory technician and has worked full time for some years. The patient has become dependent on a walker, and an electric wheelchair for longer distances. Due to this progression, the patient has only worked part-time during the last 2 years. During the last 3 years, she has experienced recurrent paresthesias in both legs. There was no indication of premature ovarian failure (POF). Follicle-stimulating hormone and luteinizing hormone levels were normal.

At age 27 years, the patient's examination was characterized by predominant axial ataxia, mild dysarthria, and dysmetria. At this point, her scale for the assessment and rating of ataxia (SARA) score was 12.5 (range 0–40, normal 0–3). Oculomotor apraxia (OMA) was absent but broken smooth pursuit and nystagmus were evident, and both her convergence and optokinetic nystagmus (OKN) were impaired. The rest of the examination demonstrated areflexia, but pyramidal signs, other movement disorders, muscle atrophy, and telangiectasias were absent. Two years later her SARA score was 15.5 and her functional stage on the Friedreich ataxia (FRDA) rating scale was 4 (range 0–6), corresponding to moderate disability. The main features of the examination are shown in a Supplementary Video.

Routine tests and a screening for neurometabolic diseases were normal; however, AFP was elevated at 12 μg/L (normal value < 8). Albumin, cholesterol, immunoglobulin, and creatine kinase (CK) levels were normal. Antibodies against human T-cell lymphotropic virus type 1 (HTLV-1) and for paraneoplastic-/autoimmune-mediated ataxias and celiac disease were absent. A second MRI at age 27 revealed progression of cerebellar atrophy (Figure 1), and this atrophy was moderated and extended into the medial cerebellar peduncles.

Mutations for common hereditary ataxias, including FRDA and the polyglutamine spinocerebellar ataxias (spinocerebellar ataxia 1, 2, 3, 6, and 7 and dentatorubropallidoluysian ataxia) were ruled out at a different center. Testing for *POLG* mutations was negative. A targeted single-gene genetic test identified the previously described pathogenic mutations c.5308_5311del (pGlu1770Ilefs*) and c6029A>G (p.Asn2010Ser) in senataxin (*SETX*).[1,2] Each parent harbored one of the heterozygous *SETX* mutations. The patient was subsequently diagnosed with AOA2.

Discussion

The presence of polyneuropathy and elevated AFP significantly narrows the differential diagnosis in patients with early-onset cerebellar ataxia. In this case, a targeted gene analysis was justified. AOA2 is, after FRDA, the second most common genetic ataxia in some parts of Europe.[3] Furthermore, AOA2 is panethnic with clusters occurring in some areas, such as Quebec.[3,4] Age of onset (AO) is usually during puberty (median 14 years) and the disease is slowly progressive.[2–8] Anheim et al. found that AO in AOA2 correlates with disease duration (DD).[2] Despite its name, OMA is not a universal trait in AOA2 or ataxia-telangiectasia (A-T); OMA occurred in ~50% and strabismus in ~12% of patients with AOA2 in the largest cohort analyzed to date (90 patients).[2] In contrast, OMA was absent but strabismus found in 30% of patients in a French-Canadian cohort.[4] OMA is more common in AOA1 and ataxia with oculomotor apraxia 4 (AOA4) but both conditions have earlier AO (<10 years) than AOA2.[2,5] A thorough study using video-oculography (VO) could not distinguish AOA2 from A-T or AOA1.[9] On the other hand, strabismus can precede ataxia and its presence is highly suggestive of AOA2.[2,3] In addition, early AO in AOA2 is associated with a higher frequency of strabismus.[2] Corrective surgery for strabismus in our case had only transient benefit, but there is no systematic evaluation of this treatment in patients with AOAs and A-T.

Hyperkinesias, such as dystonia, myoclonus, or chorea, are common in AOA1 but more variable in AOA2. In contrast to AOA1 and the classic form of A-T, cognition is usually unaffected in AOA2.[3] Pyramidal signs occur in ~20% of patients with AOA2[2] but were absent in the case we describe here.

Cerebellar atrophy is very common if not a universal trait in AOA2 ranging from 96 to 100%.[2–4,7,8] In the patient, we describe cerebellar atrophy that was progressively more pronounced in the vermis. A similar high frequency of axonal polyneuropathy has been demonstrated in different cohorts.[2–4,6–8] Of note, the underlying polyneuropathy is similar in AOA1, AOA2, AOA4 and A-T which illustrates the importance of determining albumin, cholesterol, and immunoglobulin levels. Hypoalbuminemia and hypercholesterolemia with normal AFP are the hallmarks of AOA1.[10] Immunoglobulin levels are usually reduced in A-T. In this context, the degree of AFP elevation is a more useful diagnostic clue to distinguish AOA2 and A-T with higher levels

(tenfold elevation) seen in the latter condition. However, 5% of patients with A-T have normal AFP levels.[3] Elevation of AFP is progressive in A-T but mild and stable over the course of disease for AOA2.[2,11] Importantly, AFP elevation is an almost universal feature of AOA2 (present in 99–100%) but it does not correlate with DD or disease severity in AOA2, preventing its use as a disease biomarker.[2,4,8] AFP is still a very useful diagnostic tool for A-T and AOA2,[12,13] although sometimes repeated measurements are required before elevated levels can be established.[2] Other clinical clues favoring AOA2 are the lack of immunodeficiency, pulmonary symptoms, and family history of cancer. All these features and increased sensitivity to ionizing radiation are hallmarks of A-T. In addition, various endocrine abnormalities affect patients with A-T, whereas POF or hypogonadism affects some patients with AOA2.[2,6,14] Furthermore, infertility has recently been reported in patients with AOA2.[15] Obesity has been described in one-third of patients with AOA4 but not in AOA2 or A-T.[16,17] In addition, some patients with AOA4 display elevated AFP (1.5–4-fold) but the majority have hypercholesterolemia and hypoalbuminemia.[16,17] AFP is also elevated in patients from the only family diagnosed with ataxia with oculomotor apraxia type 3 (AOA3) and very rarely in AOA1.[17,18] Few reports have described elevated AFP in mitochondrial depletion syndromes but longitudinal studies assessing AFP levels are lacking.[19–21] Some patients with AOA2 also have elevated CK levels, mild hypoalbuminemia, or hypercholesterolemia. AFP is also elevated in germinal tumors potentially linking ataxia to paraneoplastic cerebellar degeneration (PCD). However, since PCD is usually associated with subacute onset and rapid progression, it was not part of the differential diagnosis in our case. In contrast to classic A-T, patients with AOA2 may survive to old age, but variable degree of hyperkinesias occurs in both conditions more commonly in A-T.[2,3] Moreover, variant ataxia-telangiectasia (vA-T) is sometimes associated with generalized dystonia and absence of ataxia illustrating the wide phenotypic variability in the spectrum of mutations in the ataxia-telangiectasia mutated (*ATM*) gene.[22–26]

SETX encodes for a DNA/RNA helicase with multiple functions including maintenance of genomic stability, DNA damage response (DDR), transcription termination, RNA metabolism, and neurogenesis.[27] Evidence in a yeast homolog, Sen 1, indicates that it prevents accumulation of RNA/DNA hybrids (R-loops) formed during transcription. An abnormal accumulation of R-loops may play a role in neurodegeneration caused by mutated RNA-associated proteins such as ataxin-2.[27] Of note, heterozygous *SETX* mutations are also associated with juvenile motor neuron disease, amyotrophic lateral sclerosis 4 (ALS4), and tremor.[28,29] Anheim et al. found that missense mutations in the helicase domain of *SETX* were associated with a less severe AOA2 presentation than mutations outside of this domain or truncating mutations.[2] Indeed, one of the mutations (p.Asn2010Ser) in our case is located in the helicase domain (C-terminal) and may result in expression of mutant senataxin contributing to a milder phenotype. It has been proposed that *SETX* mutations associated with ALS4 are gain-of-function.[2,30] Although the mechanism linking AOA2, A-T, and AOA4 with elevated AFP is still unknown, disrupted regulation of *AFP* expression has been suggested.[30] Neither the *knockout* mouse models for *SETX* nor *AFP* feature neurological abnormalities, despite replicating the reproductive and molecular abnormalities found in patients, adding more complexity to the disease mechanism.[30] In contrast to the aforementioned ataxia diseases, AFP levels are reduced in Down's syndrome.[13]

AFP is highly expressed during normal fetal development; this expression declines after birth and reaches stable (adult) levels around age 2 years. Of note, some patients have a genetic AFP deficiency and some are predisposed to elevated levels without any pathological association.[13] Nonneurological conditions with elevated AFP include hepatocellular carcinoma, hepatitis, congenital hypothyroidism, and fetal malformations; in the past, fetal malformations were screened by analyzing maternal AFP serum levels during pregnancy.[13]

Etiological diagnosis for ataxias is crucial for proper management, prognosis, genetic counseling, and hopefully for future pharmacological trials. Treatment for AOA2 and similar disorders is largely symptomatic, and current efforts in basic research will hopefully translate into disease modifying therapies. A-T and the other conditions in the spectrum of *ATM* mutations are in this context systemic syndromes with radiosensitivity, increased risk for malignancy, severe pulmonary disease, and reduced life expectancy. So far there is no evidence for malignancy in AOA2 despite *SETX* being involved in DDR.

Current guidelines recommend testing patients with young-onset ataxia for FRDA[31] even in settings with low prevalence for FRDA such as Scandinavia.[32] In the context of ataxia with or without strabismus, polyneuropathy, and mild to moderate elevated AFP, it is reasonable to perform a targeted test for AOA2 as in the case we have described. Increasing accessibility, faster turnaround, and lower costs make either whole exome or genome sequencing reasonable options when AOA2 is hard to discern from its differential diagnosis. However, an important limitation of next-generation sequencing is that they do not detect pathological polynucleotide expansions.

Authors' contributions

Martin Paucar was responsible for patient investigation, concept, and manuscript preparation. Alexander Taylor and Marios Hadjivassiliou reviewed the case presentation and edited the manuscript for clinical content. Brent Fogel and Per Svenningsson provided supervision and critical revision for intellectual content.

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