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

Citation: Paucar M, Taylor AMR, Hadjivassiliou M, Fogel BL, Svenningsson P. Progressive ataxia with elevated alpha-fetoprotein: Diagnostic issues and review of the literature. Tremor Other Hyperkinet Mov. 2019; 9. doi: 10.7916/tohm.v0.708

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
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. In contrast to AOA1 and ataxia with oculomotor apraxia 4 (AOA4) but both conditions have earlier AO (<10 years) than AOA2. A thorough study using video-oculography (VO) could not distinguish AOA2 from A-T or AOA1. On the other hand, strabismus can precede ataxia and its presence is highly suggestive of AOA2. In addition, early AO in AOA2 is associated with a higher frequency of strabismus. 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.

Cerebellar atrophy is very common if not a universal trait in AOA2 ranging from 96 to 100%. 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. 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. Immunoglobulin levels are usually reduced in A-T. In this context, the degree of AFP elevation is more useful diagnostic clue to distinguish AOA2 and A-T with higher levels.

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. Furthermore, AOA2 is panethnic with clusters occurring in some areas, such as Quebec. Age of onset (AO) is usually during puberty (median 14 years) and the disease is slowly progressive. Anheim et al. found that AO in AOA2 correlates with disease duration (DD). 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). In contrast, OMA was absent but strabismus found in 30% of patients in a French-Canadian cohort. OMA is more common in AOA1 and ataxia with oculomotor apraxia 4 (AOA4) but both conditions have earlier AO (<10 years) than AOA2. A thorough study using video-oculography (VO) could not distinguish AOA2 from A-T or AOA1. On the other hand, strabismus can precede ataxia and its presence is highly suggestive of AOA2. In addition, early AO in AOA2 is associated with a higher frequency of strabismus. 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.
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Furthermore, infertility has been observed in affected males. Importantly, AFP elevation is an almost universal feature of AOA2 and AOA4 mutations associated with ALS4 are gain-of-function. Anheim et al. found that missense mutations 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. Although the mechanism linking AOA2, A-T, and AOA4 with elevated AFP is still unknown, disrupted regulation of AFP expression has been suggested. 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. In contrast to the aforementioned ataxia diseases, AFP levels are reduced in Down’s syndrome.

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. 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.

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 even in settings with low prevalence for FRDA such as Scandinavia. 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 Svenningson provided supervision and critical revision for intellectual content.

**Acknowledgments**

The authors are grateful to the patient for the kind participation and Dr. T. Osman for referring the patient.

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...set features. In conclusion, AFP elevation is an almost universal feature of AOA2 and AOA4 mutations associated with ALS4. Importantly, AFP elevation is highly expressed during normal fetal development; this expression declines after birth and reaches stable (adult) levels around age 2 years.

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