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Klinikinis atvejis / Case Report

Diagnostic Challenges of Ataxia with Oculomotor Apraxia Type 2 (AOA2): A Clinical Case Presentation with Literature Review

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Summary. Ataxia with oculomotor apraxia type 2 (AOA2) is an autosomal recessive cerebellar ataxia (ARCA) caused by loss-of-function mutations in the SETX gene. AOA2 is among the most frequently diagnosed non-Friedreich ARCAs in individuals across Europe, which makes it important to understand its clinical feature and laboratory findings for accurate diagnosis and patient care. This disorder typically presents during adolescence with progressive cerebellar ataxia, sensorimotor neuropathy, tremor, oculomotor abnormalities, and may also lead to infertility. Key diagnostic markers, prominent in more than 95% of patients, are elevated alpha-fetoprotein (AFP) levels and cerebellar atrophy – most commonly, in the vermis and anterior lobe of the cerebellum, as observed on brain *Magnetic Resonance Imaging* (MRI); however, definitive diagnosis is made based on genetic testing. Currently, no disease-modifying therapy exists, and disease management focuses on symptomatic treatment and rehabilitation. This article presents a case of a 29-year-old female patient with AOA2, whose diagnosis was delayed due to initially low AFP levels that became elevated only after the disease progressed. Moreover, the patient experienced unusually rapid disease deterioration, especially after contracting COVID-19 – within 12 years of symptom onset, she became wheelchair-dependent. This case illustrates the complexity of AOA2 diagnosis when early biomarkers or definitive genetic confirmation are absent, thus highlighting the value of repeated AFP evaluation over time.

Keywords: Ataxia with Oculomotor Apraxia Type 2, AOA2, ARCA, SETX gene, cerebellar atrophy, alpha-fetoprotein.

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Sunkumai diagnozuoti 2 tipo ataksiją su okulomotorine apraksija: klinikinio atvejo pristatymas ir literatūros apžvalga

Santrauka. 2 tipo ataksija su okulomotorine apraksija (AOA2) – tai autosominiu recesyviuoju būdu paveldima smegenėlinė ataksija (ARCA), kurią sukelia *SETX* geno mutacijos. AOA2 yra viena iš dažniausiai diagnozuojamų ne Friedreicho tipo autosominių recesyviųjų ataksijų Europoje, todėl, siekiant tinkamai diagnozuoti šią ligą ir paskirti tinkamą sergančiojo priežiūrą, yra svarbu suprasti jos klinikinius požymius ir laboratorinius rodiklius. Pirmieji ligos simptomai dažniausiai išryškėja paauglystėje. Pasireiškia progresuojanti smegenėlinė ataksija, sensomotorinė neuropatija, tremoras, okulomotoriniai sutrikimai, taip pat gali būti nevaisingumas. Pagrindiniai diagnostiniai žymenys, nustatomi daugiau nei 95 % pacientų, yra padidėjęs alfafetoproteino (AFP) kiekis kraujyje ir magnetinio rezonanso tyrimo (MRT) metu matoma smegenėlių atrofija – dažniausiai smegenėlių kirmine arba smegenėlių priekinėje skiltyje, tačiau galutinė diagnozė patvirtinama tik genetiniu tyrimu. Šiuo metu ligos eigą modifikuojančio gydymo nėra, todėl AOA2 gydymas yra tik simptominis ir orientuotas į reabilitaciją. Straipsnyje pristatome 29 metų moters, sergančios AOA2, klinikinį atvejį. Jai diagnozė buvo uždelsta dėl pradžioje nedidelių AFP reikšmių, kurios padidėjo tik ligai progresavus. Be to, pacientės būklė blogėjo neįprastai greitai, ypač po persirgtos COVID-19 infekcijos – per 12 metų nuo simptomų išryškėjimo ji tapo priklausoma nuo neįgaliojo vežimėlio – greičiau, nei tai įprastai būdinga AOA2 ligai. Šis klinikinis atvejis pabrėžia AOA2 diagnostikos sudėtingumą, kai ankstyvieji biožymenys nėra nustatomi, o genetiniai rezultatai negali užtikrintai patvirtinti diagnozės, ir išryškina pakartotinio AFP tyrimo atlikimo svarbą ligai progresuojant.
Raktažodžiai: 2 tipo ataksija su okulomotorine apraksija, AOA2, ARCA, *SETX* genas, smegenėlinė ataksija, alfafetoproteinas.

Introduction

Ataxia with oculomotor apraxia type 2 (AOA2; also known as spinocerebellar ataxia with axonal neuropathy-2 (SCAN2), recently renamed by the *Movement Disorder Society* (MDS) as ATX-SETX) is one of many *Autosomal Recessive Cerebellar Ataxia* (ARCA) diseases. ARCAs are hereditary neurodegenerative diseases, most often occurring at a young age and affecting the cerebellum. This group of diseases causes symptoms such as cerebellar gait and limb ataxia, peripheral neuropathy, tremor, hyporeflexia, skeletal anomalies, oculomotor apraxia, and others [1–3].

AOA2 is one of the most common non-Friedreich ARCA diseases in the European population [4]. Symptoms occur during adolescence, most often before the age of 20. Disease phenotypes consist of progressive cerebellar ataxia, sensorimotor neuropathy, tremor, dystonia, dysarthria, oculomotor apraxia, strabismus, mild cognitive impairment or other subtle cognitive changes. Other important clinical features include elevated alpha-fetoprotein (AFP) levels and cerebellar atrophy on brain MRI, both of which are found in almost all patients [5–7]. AOA2 is an autosomal recessive disease caused by loss-of-function mutations in the SETX gene, which is located on chromosome 9q34. It encodes a 2677 amino-acid protein named Senataxin that plays a role in maintaining genome integrity by regulating processes like DNA repair, transcription termination, or R-loop resolution. Although the diagnosis of AOA2 is based on clinical, laboratory and neuroimaging findings, only the identification of biallelic homozygous or compound heterozygous SETX gene mutations lead to a definitive AOA2 diagnosis [8,9].

In this article, we present a unique clinical case of a young ataxic patient whose diagnosis of AOA2 was significantly delayed due to initially normal AFP levels, which only became elevated during disease progression. The patient also experienced unusually rapid disease deterioration, particularly after contracting COVID-19 infection, becoming dependent on wheelchair use after just 12 years of symptom onset.

Case Report

The patient is a 29-year-old Caucasian female born to non-consanguineous parents with unremarkable family history. She was born after a normal pregnancy and delivery and had normal developmental milestones. However, at around 16 years old, imbalance and gait instability appeared, followed by more frequent falls and tripping on unstable ground. Later, she noticed shaking in her hands and left leg. According to the patient and her family, the symptoms appeared gradually, without a clear causative factor. In 2017, the patient was evaluated by a neurologist and geneticist. Given that ataxia was the predominant symptom, genetic testing for Friedreich's ataxia (FA) was performed. The diagnosis was ruled out as no GAA repeat expansions were detected. At the same year, brain MRI demonstrated atrophy of cerebellum, supracerebellar arachnoid cyst and small non-specific white matter changes in the cerebral hemispheres (Fig. 1). *Electroneuromyography* (ENMG) was performed; it indicated sensory polyneuropathy of the legs and left peroneal nerve axonopathy. The clinical diagnosis of early cerebellar ataxia and sensory polyneuropathy was established based on clinical and electrophysiological findings.

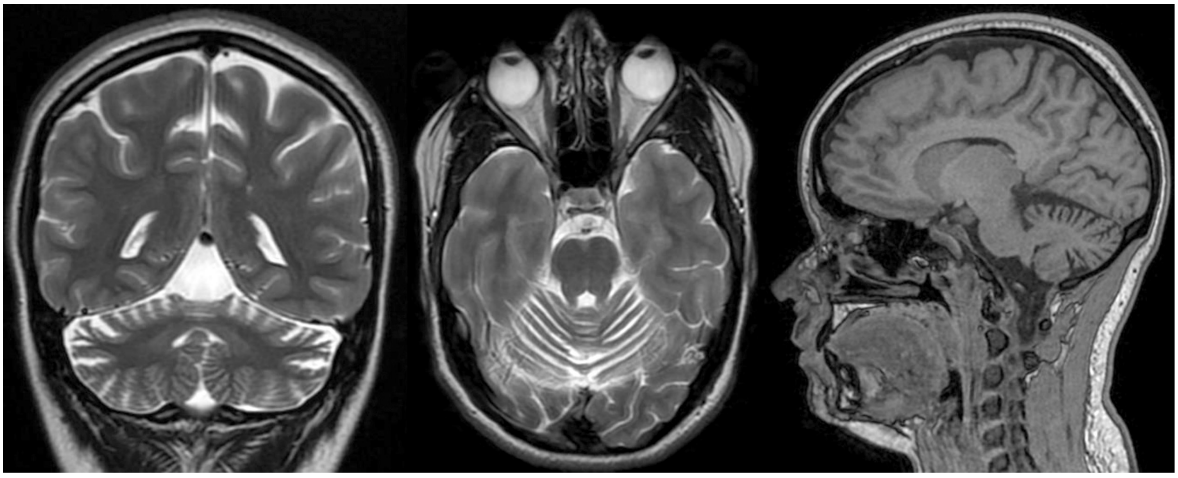

Figure 1. Non-contrast brain MRI of the patient: cerebellar atrophy seen on coronal MRI T2 (left), axial MRI T2 (middle) and sagittal MRI T1 (right) views.

In the following years, the condition of the patient deteriorated gradually, and she had multiple bone fractures because of even more frequent falls. However, repeated brain MRI revealed no new pathological findings. In 2020, molecular genetic testing was conducted for the second time using targeted *Next-Generation Sequencing* (NGS) with the *Ion AmpliSeq™ On-Demand IAD147978 Panel*. The analysis identified two SETX gene variants: *NM_015046.7:c.675dupC(;) 7364A>G*. After these results, the diagnosis was revised to neuropathy with hereditary ataxia. Treatment with Amantadine was initiated; however, due to lack of improvement, the treatment was discontinued after 4 months.

After contracting COVID-19 in 2021, the patient's condition worsened significantly. She started to sway while sitting and had trouble maintaining her trunk straight; also, she started to notice involuntary head movements. The patient was no longer able to walk independently and could only do so with a walker. Additionally, in the same year, her eyesight worsened, the patient complained of double vision, which increased when using corrective glasses. She began experiencing difficulties with her speech. At the same year, psychological evaluation was performed, and the

patient was diagnosed with adjustment disorder, and later with insomnia. Mirtazapine (15 mg), Duloxetine (30 mg) and Triazolam (250 μg) were prescribed.

In 2022, genetic testing of the patient's parents using Sanger sequencing revealed that both parents carried SETX gene mutations: father was found to be a carrier of a likely pathogenic SETX variant, *NM_015046.7(SETX):c.[675dup];[675=]*, and mother was determined to be a carrier of a variant of uncertain significance, *NM_015046.7(SETX):c.[7364A>G];[7364=]*. These findings indicate that the patient's variants are in trans configuration; however, combined with the earlier testing results of the patient, they do not provide definitive genetic confirmation of AOA2, since one of the variants is of an uncertain clinical significance. Therefore, the AOA2 diagnosis was made based on previous clinical, laboratory, and radiological findings.

The most recent physical and neurological examinations demonstrated multiple abnormalities across several domains. Oculomotor dysfunction included impaired voluntary gaze control, hypometric horizontal and vertical saccades, direction-changing horizontal nystagmus, and convergent strabismus with associated diplopia. Cerebellar signs were prominent, manifesting as dysarthria, dysphonia, trunk and head titubation, intention tremor of the hands, dysmetria, dysdiadochokinesia, and ataxic gait. Both finger-to-nose and heel-to-shin tests were abnormal. Motor examination revealed symmetric weakness of the upper and lower extremities (MRC grade 4/5), while sensory testing demonstrated impaired proprioception and vibratory sensation in the lower limbs. Laboratory investigations showed a progressive elevation of serum alpha-fetoprotein (AFP) levels, increasing from an initial value of 7.68 μg/L to 30.17 μg/L (four times the upper limit of normal). Electroneuromyography confirmed progressive sensory axonal neuropathy affecting all four limbs.

Approximately 12 years after the initial symptoms, the patient's condition is currently progressively deteriorating. The patient has severely limited mobility and self-care abilities. She requires continuous nursing care and assistance. Her movement is significantly impaired; she can walk indoors only with a walker and can leave the house independently only when accompanied by family members. For longer distances, she relies on a wheelchair. She is unable to perform daily household tasks, prepare meals, or dress without assistance. As of today, her Barthel Index score for Activities of Daily Living (ADL) is 50, and her score of the Scale for the Assessment and Rating of Ataxia (SARA) is 26.

Pathogenesis

The pathogenesis of AOA2 centers on mutations in the SETX gene, which encodes Senataxin, located on chromosome 9q34 [8]. Senataxin is a 2677 amino-acid protein that has a DNA/RNA helicase domain (HD) in the C-terminal, which is involved in various aspects of RNA processing, DNA repair and genome stability maintenance. Research has highlighted Senataxin's roles in transcription termination, resolution of R-loops, preventing DNA damage in oxidative stress, autophagy and antiviral response [8–12].

In AOA2, more than 100 mutations in the SETX gene are known, and they can occur throughout the gene. These include missense, nonsense, frameshift or truncating mutations. A review of 57 studies revealed that the majority of AOA2 disease-causing mutations are missense variants, followed by frameshift mutations [7,13]. Interestingly, in AOA2, recessive mutations in the SEXT gene lead to a loss of function of Senataxin, whereas dominant mutations in the same gene can cause ALS4 and result in a gain of the function effect [11,14]. SETX shows widespread neuronal expression, with its highest concentrations found in the hippocampus and cerebellum – particu-

larly in Purkinje cells, as seen in the mouse brain [15]. Loss of function mutations in SETX lead to the accumulation of R-loops – DNA/RNA hybrids. This R-loop build-up results in genome instability – i.e., cells become more sensitive to oxidative stress, show increased and persistent DNA double-strand breaks, and exhibit impaired or slower repair of these breaks [10,16]. Additionally, loss of SETX was associated with disrupted autophagic processes, resulting in the buildup of ubiquitinated proteins which are linked to several neurodegenerative diseases, along with a reduced capacity to clear defective mitochondria or aggregated proteins, which further adds to cellular stress [11].

To date, numerous studies have been conducted both in mouse models and with AOA2 patients and their cells to better understand the pathophysiology of AOA2. A study conducted with SETX knockout mice revealed a reduced testis size, along with a build-up of R-loops in spermatocytes and seminiferous tubules, which led to inhibition of spermatogenesis, absence of mature sperm, and ultimately, mice infertility [16]. Similarly, in a later study of infertile AOA2 male patients, histological analysis of the testis revealed an increased number of tubules with R-loop accumulation, confirming that SETX also plays a role in fertility [17]. However, a major difference between $SETX^{-/-}$ mice and AOA2 patients was that the common neurological symptoms and structural brain abnormalities observed in AOA2 were absent in SETX mutant mice, and no presence of R-loops was found in the cerebellum [16]. Other research is trying to find a link between senataxin mutations and AOA2 phenotype. In a study by Anheim et al. involving 90 AOA2 individuals, pyramidal signs were found to be more common in patients with missense mutations in the SETX gene compared to those with deletion or truncating mutations. Moreover, patients with missense mutations located in the helicase domain exhibited higher rates of dystonia and pyramidal signs than those with mutations outside the HD or deletions and truncating mutations, but, despite this, the AOA2 phenotype in the HD missense group was generally less severe [7]. These findings illustrate the complexity of AOA2 pathogenesis and suggest that not only the mutation type, but also its localization and other yet unknown factors may influence the disease phenotype, thereby highlighting a need for further research.

Clinical Symptoms

AOA2 typically manifests in adolescence, at around 15-years-old, with a symptom onset raging from ages 5 to 25 [4,6,7]. The clinical presentation of AOA2 is diverse, with several hallmark features.

The most prominent and early symptom of AOA2 is progressive cerebellar ataxia. In a study of 18 patients from 6 families with AOA2, gait ataxia was the first symptom in 78% of patients, and, eventually, it developed in all of them [4]. Similarly, a study by Nanetti et al. involving 22 Italian patients from 21 families found that all 13 patients who carried SETX mutations experienced gait difficulties, with 11 of them reporting this symptom as the initial manifestation [18]. Other primary disease signs in these studies included strabismus, mild choreic movements, dystonia or postural tremor, with a frequency ranging from 11% to approximately 15% [4,18].

Cerebellar ataxia is one of many symptoms of cerebellar degeneration observed in AOA2, along with action tremor affecting the trunk or limbs, disdiadochokinesis, a reduced muscle tone, dysarthria or scanning speech, as well as oculomotor abnormalities such as fixation instability, inaccurate saccades, and nystagmus [19]. The disease name itself suggests another eye movement abnormality, *Oculomotor Apraxia* (OMA), which is characterized by compensatory head thrusts due to difficulty with horizontal saccade initiation [18]. However, it is noteworthy that OMA

may be absent in the majority of patients, making it more frequent in other autosomal recessive ataxias like AOA1 (86%), ataxia telangiectasia-like disorder – ATLD (90%), AOA4 (100%) and ataxia telangiectasia – AT (100%) [20]. For example, a major study of 90 AOA2 positive patients by M. Anheim et al. revealed that only a fraction above half of the cases (51%) had OMA, while in a study by C. Criscuolo et al., OMA was found in 20% of its patients [7,21]. Interestingly, none of the 24 French-Canadian AOA2 patients in A. Duquette et al.'s study presented with oculomotor apraxia [22].

The majority of AOA2 patients develop axonal sensorimotor neuropathy. This condition is characterized by a decline in tendon reflexes, loss of vibratory sensation in the distal parts of the limbs, and motor impairments. Electrophysiological tests often reveal abnormalities in nerve conduction, further supporting the diagnosis [7]. This observation is supported by research involving nineteen patients from seven unrelated Algerian families, where 90% of the research subjects exhibited these symptoms [23]. Moreover, a comprehensive review covering fifty-seven studies on AOA2 patients with SETX variants found that 94.6% suffered from peripheral neuropathy [13]. Moreover, sensory neuropathy can lead to pes cavus and skeletal deformities, such as scoliosis [23]. The occurrence of pes cavus in populations with AOA2 varies significantly, ranging from approximately 34% to, in some cases, as high as 92% [13,18,23].

Along with the main symptoms, some individuals with AOA2 may experience other non-specific signs, including cognitive impairment, menopause, or infertility. Cognitive impairment is usually mild in AOA2 patients. While most individuals maintain normal intellectual abilities, subtle deficits in executive functions, memory and processing speed have been reported in some cases [4,21]. Reproductive dysfunction can affect both male and female patients. There are several cases, which suggests that AOA2 is linked with elevated levels of FSH and LH and an early menopause (occasionally, a premature ovarian failure) in females with SETX mutations as young as a 21-year-old [24]. In a study of 3 Italian sisters by Mancini et al., it was found that all of them had a premature menopause in their early 30s; also, an article covering 57 studies on AOA2 patients with SETX variants discovered that 10 females, including their case patient, presented with either an early menopause, FSH and LH imbalances, or polycystic ovarian syndrome [13,25]. As well as females, male AOA2 patients also have symptoms that cause infertility. Becherel et al.'s study showed that all 3 observed male patients with SETX mutations had sperm abnormalities, manifesting as azoospermia or oligospermia with severely impaired sperm motility, ranging from 73% to 100% non-motile sperm [17]. These findings highlight the importance of monitoring reproductive health in AOA2 patients for early intervention.

Diagnosis

A diagnosis of AOA2 can be made based on clinical, laboratory and neuroimaging findings, however, a definitive diagnosis requires genetic testing of the SETX gene [8].

The main laboratory finding in AOA2 is elevated alpha-fetoprotein (AFP) levels. This elevation is present in the majority of patients – e.g., in a study by Anheim et al., as many as 99% of patients with AOA2 had elevated AFP levels, with a median concentration of 31 μg/l [7]. In young ataxic patients with polyneuropathy and/or oculomotor apraxia, elevated AFP levels can aid in differentiating between similar ARCAs; AFP levels between 15–65 μg/l indicate AOA2, while AFP levels above 65 μg/l suggest AT as the likely diagnosis [20,25]. A cut-off value of 7 μg/l or higher has been suggested as a useful threshold for deciding when to perform SETX gene testing in young non-Friedreich ataxia non-AT ataxic patients – with less than 1% chance of missing

an AOA2 diagnosis [7]. Interestingly, asymptomatic heterozygous SETX mutation carriers could also have slightly elevated AFP levels [26]. Although AFP levels generally remain stable during the symptomatic phase of the disease, some patients may develop elevated levels years after initially normal values. Therefore, a normal AFP level in an ataxic patient with cerebellar atrophy does not exclude an AOA2 diagnosis, and laboratory values should be reassessed over time [4,7]. Additionally, elevated serum creatine kinase levels have been observed in some patients, with studies reporting increases in up to 20% of cases [22,27]. Other laboratory findings may include elevated immunoglobulins, hypercholesterolemia, hypoalbuminemia, although these are less consistently observed [4,27].

Neuroimaging, particularly *Magnetic Resonance Imaging* (MRI), reveals cerebellar atrophy in almost all AOA2 patients (95–100% of cases). The most prominent diffuse atrophy is seen in the vermis and anterior lobe of the cerebellum, although it can range from isolated cerebellar involvement to more extensive pontocerebellar atrophy [4,7,13,18,22,23,28]. This cerebellar degeneration develops early in AOA2 and is often detectable in young or minimally symptomatic patients, and tends to stabilize after several years of disease progression [7,23]. Interestingly, a new MRI finding in AOA2 has been identified when using *Susceptibility-Weighted Imaging* (SWI). On SWI MRI, iron accumulation in the dentate nucleus typically appears as a hypointense signal, which is a sign found in patients with Friedreich's ataxia as well as in healthy older individuals. However, this feature is absent in patients with AOA2, and it has a sensitivity and specificity of 100% for AOA diagnosis. This finding persist throughout disease progression regardless of the patient's age or disease duration and is a unique marker which differentiates AOA2 from other neurodegenerative diseases [28,29]. In addition to these MRI findings about the central nervous system, nerve conduction studies and *electromyography* (EMG) provide additional diagnostic information about the peripheral nervous system. These electrophysiological tests generally show axonal sensory and motor peripheral neuropathy, with absent or reduced sensory nerve action potentials, undetectable or decreased compound muscle action potential amplitudes and normal to mildly decreased motor conduction velocities [18,20,24,30]. Importantly, in a study of 90 AOA2 patients, all had either cerebellar atrophy or peripheral neuropathy, suggesting that an AOA2 diagnosis with the absence of both findings is unlikely [7].

Conclusive diagnosis of AOA2 requires genetic testing of the SETX gene. Given that AOA2 has an autosomal recessive inheritance pattern, the disease is caused by either biallelic homozygous or compound heterozygous mutations. When clinical examination strongly suggests AOA2, targeted gene testing is performed, while non-specific or overlapping phenotypes require *Whole Exome Sequencing* (WES) or even whole genome sequencing (WGS) [7,13,25,30,31]. The diagnosis can only be confirmed if genetic testing detects biallelic pathogenic or likely pathogenic variants in SETX, whereas variants of uncertain significance neither support nor rule out the diagnosis [32].

Treatment

No specific treatment is available for AOA2, and therefore the management of the disease is mainly symptomatic. Although pharmacological treatment can help alleviate specific symptoms, much of the treatment focuses on improving the patient's quality of life through physiotherapy, speech therapy, occupational therapy as well as by adapting the environment and daily tools to meet the day-to-day needs of the patient. Medications for AOA2 patients may include propranolol as a first-line treatment for tremors, focal dystonia can be managed with local botulinum toxin injections, while eye symptoms such as nystagmus may respond to gabapentin or baclofen.

Additional treatments may include the use of prisms for diplopia, dietary supplements in cases of severe dysphagia with weight loss or surgical intervention if more conservative approaches are ineffective [33].

There are various trials and pilot studies that look for different medical or therapy treatments for ataxia or other AOA2 symptoms. A randomized, double-blind, placebo-controlled pilot trial of riluzole for cerebellar ataxia found that riluzole 100 mg/d is probably effective for symptomatic therapy of cerebellar ataxias of various etiologies, with the ICARS score decreasing by at least 5 points at 8 weeks (Class I evidence) [34]. Another quasi-experimental pilot study examined strategic *Balance-Based Torso-Weighting* (BBTW) in patients with cerebellar ataxia and found it to be beneficial for improving stability while standing or reducing body sway [35]. However, these and other pilot studies on ataxia treatments involved only small numbers of patients, and therefore evidence for their effectiveness is still limited, thus highlighting the need for further studies.

Prognosis

Compared to other ARCAs, such as AT or AOA1, the prognosis of ataxia with oculomotor apraxia type 2 is generally more favorable as most patients require walking assistance after approximately 20 years of *Disease Duration* (DD), whereas individuals diagnosed with AT typically need a wheelchair after around 10 years, and those diagnosed with AOA1 – after about 11 years of disease progression [7]. Only a minority of AOA2 individuals become wheelchair-bound after a shorter disease duration, with some cases reporting wheelchair use after a mean DD time of about 13.6 or 15.3 years ± 3.52 [7,18]. Moreover, M. Anheim et al.'s study of 90 AOA2 patients discovered that neurological symptoms, such as strabismus, occur more often if the disease begins earlier (p=0.04). This symptom is linked to a more rapid progression of the disease compared to those patients who do not have strabismus, while OMA appeared to be associated with a slower progression of the disease [7]. Interestingly, there are cases suggesting that OMA can disappear over time, as well as extrapyramidal symptoms such as choreiform head movements, trunk dystonia or head tremor [21,23].

Conclusions

A combination of cerebellar ataxia, sensorimotor neuropathy, elevated AFP levels, especially between 15–65 μg/l, and cerebellar atrophy on brain MRI should guide clinicians toward a diagnosis of AOA2. Moreover, an increasing number of AOA2 patients experience infertility or an early menopause, making reproductive health monitoring of high importance in this population. While genetic testing of the SETX gene is essential for a definitive diagnosis and genetic counseling, these tests do not always provide conclusive results, particularly when variants of uncertain significance are identified, requiring clinicians to rely on clinical findings. There is currently no disease-modifying treatment available for AOA2, and therefore disease management consists mainly of symptomatic treatment and multidisciplinary care. This article presents a clinically challenging AOA2 diagnosis in a young patient. The characteristic AFP elevation was absent at disease onset and became notable only after the disease significantly progressed. This case highlights the importance of serial AFP monitoring over time and demonstrates the clinical value of applying the 7 μg/l threshold for performing SETX gene testing, which could have led to an earlier diagnosis in this patient. Moreover, this patient's disease progression was unusually aggressive, especially after contracting COVID-19 as the patient had to use a wheelchair within

12 years of the symptom onset, which is considerably faster than the typical 20-year timeline. The aim of this article is to emphasize the diagnostic challenges in AOA2 when the initial biomarkers are normal and genetic testing does not provide a definitive answer, highlighting the need for detailed clinical examination and follow-up testing in suspected cases.

Author contributions

Greta Galinytė: conceptualization, data curation, investigation, resources, writing – original draft.

Gintarė Baranauskienė: conceptualization, project administration, resources, supervision, visualization, writing – review and editing.

Rūta Kaladytė Lokominienė: project administration, supervision, visualization, writing – review and editing.

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