Ataxia with oculomotor apraxia type 2; an evolving axonal neuropathy

[1]Tahira N Choudry, [1]George Tofaris, [2]David Hilton-Jones, [3]Henry Houlden [4]Graham Lennox

[1]Department of Neurology, National Hospital for Neurology & Neurosurgery, Queen Square, London, UK
[1]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[2]Department of Neurology, John Radcliffe Hospital, Oxford, UK
[3]Reta Lila Weston Laboratories and Department of Molecular Neuroscience, UCL Institute of Neurology, Queen Square, London, UK
[4]Department of Neurology, John Radcliffe Hospital, Oxford, UK

Correspondence to:
[1] Tahira N Choudry. Department of Neurology, National Hospital for Neurology & Neurosurgery, Queen Square, London, UK. Email; *tahira.choudry@nhs.net*. Tel: 020 3456 7890.

Word Count:
Abstract- 150
Body- 1500

ABSTRACT:

We present a 23-year-old woman who complained of poorly fitting shoes during her adolescence, initially presenting to a Podiatrist. After extensive neurological review, she was diagnosed with Ataxia with oculomotor apraxia type 2 (AOA2). This is a progressive autosomal recessive (AR) ataxia associated with cerebellar atrophy, peripheral neuropathy and an elevated serum α-fetoprotein (AFP). Within Europe it is the most frequent AR ataxia after Friedreich's Ataxia (FA), and is due to mutations in the Senataxin (*SETX*) gene. The age of onset is approximately 15yrs.

The diagnosis of AOA2 can often be challenging. We provide a framework when presented with a young ataxic patient with or without oculomotor apraxia and review clues that will aid diagnosis. The prognosis, level of disability, cancer and immunosuppression risk all markedly differ between the conditions. Patients and their families need the correct diagnosis for genetic counselling, management and long-term surveillance with appropriate subspecialty services.

INTRODUCTION:

AOA2 is a progressive AR ataxia associated with cerebellar atrophy and an elevated serum AFP. There is an associated axonal sensorimotor peripheral neuropathy, in 90% of individuals.[2, 8] The presence of neuropathy or a raised AFP are the two most statistically significant findings in AOA2.[2]

The finding of an axonal sensorimotor peripheral neuropathy has a wide differential diagnosis. In the context of a young patient (<35 years) with emerging signs of cerebellar ataxia and oculomotor dysfunction it is vital to differentiate between the relevant AR cerebellar ataxias, with a DNA repair dysfunction and Friedreich's Ataxia (FA). We provide a review of essential features to aid the busy Neurologist.

CASE PRESENTATION:

This 23-year-old woman initially presented at the age of 17 years. She noticed her shoes were poorly fitting and it was proving difficult to find any fashionable shoe to fit. In 2009 her GP referred her to the Lead Podiatrist for Biomechanics. She noted high arched feet and bilateral clawing of the toes. She commented that her eyes were hard to focus and described poor coordination in her gait and hands. The Podiatrist instigated a referral to the Paediatric and Neurology team at her local hospital.

It transpired that over the last 3 years she had been tripping frequently. She complained of poor balance and worsening of her foot deformities. However, she had been keeping up with school sports and managing with day-to-day activities, without assistance. There was no evidence of cognitive decline. She did not complain of weakness or numbness. There were no visual, speech or swallowing problems. She had no pain or autonomic features. Systemically, she was well.

There was no family history of relevance. She had 2 sisters and a brother who were all fit and well. Her parents were unrelated. There was no past medical history of note. She had a normal delivery, reaching all her developmental milestones. She takes no regular medications. She had just completed her GCSE's. There was no smoking, alcohol or drug use.

Her general physical examination in 2009 was unremarkable. There were no neuro-cutaneous lesions. Her head, neck and upper limb neurological examination were normal. In the lower limbs she had high arches in both feet with hammertoes. Power was 5/5 in all muscle groups. Sensation was reduced in both lower limbs. There were no ankle or knee reflexes elicited. She was Romberg's Positive with an unsteady gait.

She was stable for several years. A routine follow-up in 2014 unravelled deterioration. She had difficulty opening jars. Her hands shook, when reaching a target. Her speech was slurred and her balance was markedly worse.

She was referred to the Neurogenetics clinic. New findings in her examination included finger-nose dysmetria and dysdiadochokinesia in the upper limbs. Within the lower limbs there was mild weakness 4+ of ankle dorsiflexion & eversion, vibration sensation was absent below her ankles with normal pinprick sensation.

In the head and neck exam there was a mild head tremor and slurred speech. She displayed poor saccadic initiation with slow saccades, and jerky pursuit movements. She displayed head thrusts with her eyes lagging behind head movements. She had a wide-based gait and a high-steppage gait, helped by using orthoses. She could not perform the heel-to-toe test.

INVESTIGATIONS:

Routine blood tests were unremarkable. Serum immunoglobulins, vitamin-E, lactic acid, amino acids were normal. The karyotype was 46 XX.

The nerve conduction test and EMG revealed a sensorimotor axonal neuropathy, with severe sensory abnormalities. The sensory nerve action potentials were reduced in amplitude (Sural≤1.6µV, radial 8.3µV) with normal conduction velocities of 38-59m/sec.

PMP 22 & Frataxin gene testing was negative. Molecular analysis for axonal CMT genes including *MFN2, GJB1/CX32, and MPZ,* was negative. The MRI Head displayed marked cerebellar atrophy (Fig 1). The AFP was raised, at 41 IU/Ml.

DIFFERENTIAL DIAGNOSIS:

The working diagnosis was initially Charcot-Marie-Tooth (CMT) or FA. The axonal neuropathy led to a search for CMT2. After her deterioration, AOA1, AOA2 or Ataxia Telangiectasia-like Disorder (ATLD) were considered.

The hereditary ataxia panel confirmed a molecular diagnosis of AOA2 (Table 1).

Table 1: Sequencing Analysis: Ataxia 77 gene panel

Gene name	Variant
SETX	Heterozygous for c.6729_6730delCA p. (His2243fs)*
SETX	Heterozygous for c.7121_7122delTG p. (Val2374fs)**

Courtesy of John Radcliffe Hospital, Genetics Department. Reported in literature in association with; *slowly progressive ataxia, neuropathy & oculomotor dysfunction, **slowly progressive ataxia & sensorimotor neuropathy.

MANAGEMENT:

Genetic counselling was provided with specialist genetic input. There is no treatment for the neurological disease. Physiotherapy and occupational therapy was undertaken. Special education and speech therapy can be beneficial.

DISCUSSION:

Ataxia with Oculomotor Apraxia Type 2 (AOA2)

This is a progressive AR ataxia associated with cerebellar atrophy and an elevated serum AFP. There is an associated axonal sensorimotor peripheral neuropathy in 90%.[2, 8] The aforementioned neuropathy or a raised AFP are the two most statistically significant findings in AOA2. Oculomotor apraxia is found in approximately 56%.[1] Pyramidal signs and movement disorders like head tremor, dystonia and chorea were present in a proportion. In AOA2 there is absence of cardiomyopathy, predisposition to cancer, infections and rare or absent telangiectasia.[8] It is the most frequent AR ataxia next to FA in Europe. The age of onset is approximately 15yrs.

Mutations in the *SETX* gene cause AOA2 and a dominant juvenile, amyotrophic lateral sclerosis (ALS4). Senataxin is a large protein at 2677 AA's.[12] It is produced in the brain, spinal cord & muscles. It contains a conserved DNA/RNA helicase domain towards the C-terminal, contributing to multiple aspects of gene expression, including transcription. It is likely to aid in DNA repair, DNA/RNA and R Loop processing.[7, 16]

Alpha-fetoprotein; value of testing

Studies have shown that the probability of missing AOA2 is 0.23%, if sequencing only the Senataxin gene. This is in non-FA, non-AT ataxic patients with AFP≥7 µg/l. It is recommended to test ataxic patients with AFP≥7µg/l for Senataxin gene sequencing in AOA2.[2]

Case studies suggest that AOA2 cannot be excluded in patients with ataxia and cerebellar atrophy without a raised AFP and/or polyneuropathy, as they may emerge later.[11] Repeating the AFP levels in a year is recommended.[2]

Eyes; the windows to a clearer diagnosis

Oculomotor Apraxia is characterised by a dissociation of eye & head movements in the head-free condition. The head reaches the lateral target before the eyes. It is not a true apraxia. It is important to compare the presence of oculomotor apraxia amongst the relevant AR cerebellar ataxias with a DNA repair dysfunction (table 2).

Table 2: Clues from Oculomotor function

Type of Oculomotor Dysfunction	AOA2*	AOA1*	AT**	ATLD***	AOA4****
Oculomotor Apraxia	56%	86%	100%	90%	100%
Saccadic pursuit	100%	100%	+	+	
Gaze evoked nystagmus	89%	100%	+†	+	
Square waves on central fixation		100%	85%		
Nature of saccades	Hypometric N velocity	Hypometric N velocity	Hypometric ↓/N velocity	Hypometric	
Impairment of:	Abduction		Convergence Accommodation		

*From Le Ber et al. (2003, 2004); **from Lewis et al. (1999), Shaikh et al. (2009 & 2011), Wood et al. (1992), ***from Fernet et al. (2005); **** from Bras et al 2015; † Also horizontal, vertical & torsional nystagmus (spontaneous), periodic alternating nystagmus; + = present; N-normal. AT- ataxia Telangiectasia; Ataxia Telangiectasia-like Disorder-ATLD

Clinical and lab differences between the main players; how to unravel the diagnosis

In the context of a young patient (<35 years) with emerging signs of cerebellar ataxia and oculomotor dysfunction it becomes vital to differentiate between the relevant AR cerebellar ataxias with a DNA repair dysfunction and Friedreich's Ataxia (FA). This table provides a review of essential features to aid the differential diagnosis (table 3).

Table 3: Clinical and lab differences between FA, A-T, AOA1-2, 4 & ATLD

Feature	FA*	AT **	AOA2***	AOA1***	ATLD****	AOA4†
Gene Locus/gene	9q/*FXN*	11q/*ATM*	9q/*SETX*	9p/ *APTX*	11q/*MRE11A*	19q/*PNKP*
No of patients	187	70	18	14	10	11
Age at onset, years (range)	15.5 ± 3.8 (2-51)	< 5	15.5 ± 3.8 (9-25)	6.9 ± 4.7 (2-18)	2.1 ± 1.9 (1-7)	4.3 ± 2.3 (9-1)

Disease duration until wheelchair, mean years	11	10	16	11	13	15
Gait ataxia	+	+	+	+	+	+
Neuropathy	S	SM	SM	SM	-	SM
Cardiomyopathy	+	-	-	-	-	-
Oculomotor apraxia	-	+	+	+	+	+
Chorea	-	+	22%	79%	+	
Pyramidal signs	+	-	±	-	+	±
Telangiectasia	-	+	-	-	-	-
Cancer risk	-	+	-	-	-	
MRI-cerebellar atrophy	-	+	+	+	+	+
AFP	-	↑	↑	-	-	±↑
Ig	-	↓‡	±↑	-	-	
Chol	-		±↑	↑	-	±↑
Albumin	-		±↓	↓	-	±↓

*From Durr et al. (1996); **from Stankovic et al. (1998) & Woods and Taylor (1992); ***from Le Ber et al. (2003, 2004); ****from Fernet et al. (2005); †from Bras et al 2015; ‡-Mainly IgA, IgG subclasses & IgE; + = present; - = absent or insignificant; AFP = a-fetoprotein; CT = cholesterol level; Ig = immunoglobulins, S = sensory, SM = Sensorimotor. Table adapted from Le Ber 2004

Currently 4 subtypes of AOA have been delineated. The distinguishing features of AT and ATLD are the presence of immunodeficiency, sensitivity to ionising radiation and chromosomal instability, absent in AOA subtypes. In AOA there is no predisposition to cancer and rare or absent telangiectasia, unlike in AT.[8]

AT and ATLD have a younger age of onset than AOA2. Clinical progression in AOA2 is gradual and functional neurological defects are less severe than in AT. The increased AFP in AT is usually 10 times the normal upper limit, compared to 5 times the normal upper limit in AOA2.

There is a strictly sensory neuropathy in FA.[5] Severe cerebellar atrophy on MRI is not common in FA, although there may be some cervical dorsal column loss. There is no cardiomyopathy and corticospinal tract involvement is infrequent, in AOA2.

AOA4 is secondary to *PNKP* mutations. PNKP is an enzyme involved in multiple pathways of DNA repair. [3] AOA4 is the most frequent form of AR ataxia in the Portuguese population, after FA. Most individuals initially present with dystonia. Ataxia and oculomotor apraxia were the next most common symptoms. All had a polyneuropathy, with early generalised areflexia, distal muscle wasting and weakness. Cognitive impairment and dementia were also present in some.[3] AOA4 and AOA1 both have prominent extrapyramidal features like chorea or dystonia and a more rapid progression than AOA2.

AOA3 is due to mutations in the *PIK3R5* gene. This encodes a regulatory protein that interacts with downstream enzymes implicated in signal transduction pathways regulating cell survival, growth, metabolism and immune function. [1] Four siblings with AOA3 were identified in a consanguineous Saudi Arabian family. They presented with ataxia and oculomotor apraxia, with negative *SETX* gene testing. They all had cerebellar atrophy and a moderately severe axonal sensory polyneuropathy. [1]

Neuropathy is more severe in AOA1. The functional prognosis is better in AOA2 than in AOA1, with longer disease duration until becoming wheelchair-bound (table 3). A case report of AOA4 details how an initial diagnosis of axonal CMT or a CMT4 mimic was considered.[13] Further to this our case demonstrates that it would be useful to include AOA2 testing in a neuropathy gene panel.

Key Points:

- AOA2 is a progressive AR ataxia associated with cerebellar atrophy, peripheral neuropathy and elevated serum AFP
- **AOA types 1-4**, AT and ATLD are the main AR cerebellar ataxias, linked with oculomotor apraxia
- Identify those young (<35yrs) ataxic patients with AFP≥7 µg/l, for Senataxin gene sequencing
- AOA2 should be included in a neuropathy gene panel

Acknowledgments and conflicting interests:
Acknowledgment and special thanks to the patient and her mother for their cooperation with filming of the video and writing of the case report.

Acknowledgment and thanks to Dr Andrea H. Németh, Nuffield Department of Genetics, University of Oxford, for specialist Genetic input.
Competing interests: None declared
Patient consent: Obtained
Funding: Nil

Contributors:
TC wrote the first drafts of the manuscript and revised for submission for publication. GL & DHJ were lead clinicians for the patient and reviewed and revised the manuscript. GT and HH supervised, reviewed and revised the manuscript.

Fig 1 MRI Head- T2 Coronal and sagittal views, showing marked cerebellar atrophy

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