Early Onset Dementia in Ataxia Associated with Ocular Apraxia Type 1 (AOA1)

Sir,

Ataxia with oculomotor apraxia type 1 (AOA1) belongs to a group of autosomal recessive cerebellar ataxias (ARCAs) characterized by early-onset cerebellar ataxia with oculomotor apraxia (OMA), sensorimotor axonal polyneuropathy, movement disorders, and elevated alpha-fetoprotein (AFP).[1,2] There are several types of AOA the most common types are 1, 2, and 4 [Table 1].

AOA1 results from a mutation in the aprataxin (*APTX*) gene in chromosome 9p13.[3]

The onset has been reported from 4 to 29 years. The duration of the disease until wheelchair use ranges from 2 to 38 years.[3]

Undetermined intellectual disability has been remarked in 51% of patients.[3] Overall, cerebellar ataxia syndromes demonstrate a specific cognitive impairment pattern described as a cerebellar cognitive affective syndrome (CCAS).[4]

We report a 60-year-old woman of Netherlands origin with AOA1, who was intellectually intact until the 58th year of age when she presented an early onset (*with onset at an age of less than 65 years old)* progressive dementia syndrome more compatible with Alzheimer dementia (AD) than with a CCAS.

Table 1: Clinical and biochemical features of cerebellar ataxias with oculomotor disturbances and sensorimotor neuropathy. The number of crosses expresses the comparative severity and incidence of the findings

	AOA1	AOA2	AOA4
Autosomal recessive	+	+	+
Cerebellar atrophy	+	+	+
Video-oculography findings	+	+	+
Sensorimotor neuropathy	+	+	+
Early age onset	++	+	+++
Movement disorders	++	+	++
Pyramidal involvement	+	+	+
Dysarthria	+	+	+
Severe walking disability	+	+	+
Pes cavus	+	+	+
AFP	+	++	++
Hypoalbuminemia	++		+
Hypercholesterolemia	++		+
Scoliosis	+	+	+
Intellectual disability	+	+	+
Epilepsy		+	
Obesity			+
Mutated genes	Aprataxin (*APTX*)	Senataxin (*SETX*)	*PNKP*

AOA1: ataxia with oculomotor apraxia type 1, AOA2: ataxia with oculomotor apraxia type 2, AOA4: ataxia with oculomotor apraxia type 4

Her medical history was intact until the age of 20 when she presented a slowly progressive tremor and gait disturbance, gradually accompanied by muscle weakness and sensory disturbance of the limbs. She started using a wheelchair in her 40s.

She mentioned a history of severe gait disturbance syndrome in her mother's sister.

Her Mini-Mental-State Examination (MMSE) score was 23/30, the Instrumental Activities of Daily Living (IADL) score was 6/8 while Hopkins Verbal Learning Test-Revised revealed decreased verbal learning, memory, and recall. Deficits in visuospatial memory and perception were detected with Brief Visuospatial Memory Test-Revised, and affected executive functions were revealed by the Clock Drawing Test and Trail Making Test Form B. A Geriatric Depression Scale (GDS) score of 7 was compatible with mild depressive symptomatology. No apathy or disinhibition was remarked.

Brain MRI demonstrated median temporal and parietal lobe atrophy of grade 2 and a reduced volume of hippocampi grade 1 on Scheltens *et al.*'s scale. Cerebellar atrophy was also present.

Ocular movements were moderately limited in all directions with horizontal gaze-evoked nystagmus. Hypometric rightward saccade with increased latency was found on recordings by video-oculography.

Distal dominant muscle atrophy, sensory disturbance of glove and stocking type, generalized areflexia, and intentional tremor of the upper limbs were observed.

Routine blood studies showed a decreased albumin (3.2 g/dL) level, increased total cholesterol (283 mg/dL), and mildly elevated AFP levels of 7 μg/L in the serum.

The needle electromyogram of the upper and lower extremities showed reduced recruitment and long-duration, polyphasic muscle units. Nerve conduction studies revealed severe axonal sensory-motor polyneuropathy.

The cerebrospinal fluid (CSF) biomarker panel was highly indicative of AD: low concentrations of the amyloid-β 1-42 peptide (432 pg/mL, normal values ≥849), high concentrations in total tau (470 pg/mL, normal values ≤195), and phospho-tau (68 pg/mL, normal values <61) were observed.[5] An ApoE genotyping test revealed an E4/E4 model, as further support for the AD.[6]

Regarding the clinical and biochemical features, AOA1 was the most probable inherited cerebellar ataxia syndrome, as it is demonstrated in Table 1.

DNA sequencing for AOA1 showed that the patient was compound heterozygous for the Trp279* and Lys197Gln

Table 2: Different cognitive and neuroradiologic features in SCA series,[4] AOA1 (our patient), AOA 2 (case study)[7]

	SCA	AOA1	AOA2
Memory decline	-	++	-
Learning decline	+	++	+
Daily activities	+	++	+
Behavior disorders	++	+	++
Executive dysfunction	+++	+	++
Verbal fluency	+++	+	++
Visuospatial dysfunction	+++	+	++
Cerebellar atrophy	+	+	+
Cortical atrophy	±	++	-

The number of crosses expresses the comparative severity and incidence of the findings

mutation in the *APTX* gene. The same mutation status has been previously described in another Netherlands patient.[3]

The patient's only daughter showed no abnormal findings and denied genetic testing. The no longer alive patient's parents were not related as second cousins or closer.

Consistent with other investigations of patients with cerebellar ataxias, our patient showed executive dysfunction, decreased performance on verbal fluency tests, and affected visuospatial short-term memory[3,7] [Table 2].

Simultaneously, she scored poor on learning and memory tests.[3] Additionally, neuroradiologic and biomarkers evidence was compatible with AD.[4,5]

Our case indicates that besides the expected CCAS, other types of early dementia syndromes, such as AD can also occur or co-occur in AOA1 patients. We conclude that any kind of early-onset cognitive decline should be thoroughly investigated even in these rare inherited cerebellar syndromes.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient and her daughter have given their consent for clinical information to be reported in the journal. They understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

Anastasiou I. Aikaterini, Georgios I. Papagiannis[1,2], Kontoangelos A. Konstantinos[3], Konstantina G. Yiannopoulou[4]

Medical School of Athens, National and Kapodistrian University of Athens, [1]Orthopaedic Research and Education Center "P.N. Soukakos", Biomechanics and Gait Analysis Laboratory "Sylvia Loannou"; "Attikon" University Hospital, [2]1st Department of Orthopaedic Surgery, Medical School, National and Kapodistrian University of Athens, [3]1st Department of Psychiatry, National and Kapodistrian University of Athens, Eginition Hospital, [4] Department of Neurological, Henry Dunant Hospital Center, Athens, Greece

Address for correspondence: Dr. Konstantina G. Yiannopoulou, MD, PhD, Department of Neurological, Henry Dunant Hospital Center, 107 Mesogeion Avenue, Athens 11526, Greece.
E-mail: k.giannopoulou. 14@hotmail.com

References

1. Mariani LL, Rivaud-Péchoux S, Charles P, Ewenczyk C, Meneret A, Monga BB, *et al.* Comparing ataxias with oculomotor apraxia: A multimodal study of AOA1, AOA2 and AT focusing on video-oculography and alpha-fetoprotein. Sci Rep 2017;7:15284.
2. Dumitrache LC, McKinnon PJ. Polynucleotide kinase-phosphatase (PNKP) mutations and neurologic disease. Mech Ageing Dev 2017;161:121-9.
3. Renaud M, Moreira M, Monga BB, Rodriguez D, Debs R, Charles P, *et al.* Clinical, biomarker, and molecular delineations and genotype-phenotype correlations of ataxia with oculomotor apraxia type 1. JAMA Neurol 2018;75:495-502.
4. Giocondo F, Curcio G. Spinocerebellar ataxia: A critical review of cognitive and socio-cognitive deficits. Int J Neurosci 2018;128:182-91.
5. Niemantsverdriet E, Valckx S, Bjerke M, Engelborghs S. Alzheimer's disease CSF biomarkers: Clinical indications and rational use. Acta Neurol Belg 2017;117:591-602.
6. Zhao N, Liu CC, Qiao W, Bu G. Apolipoprotein E, Receptors, and Modulation of Alzheimer's Disease. Biol Psychiatry 2018;15:347-57.
7. Klivényi P, Nemeth D, Sefcsik T, Janacsek K, Hoffmann I, Haden GP, *et al.* Cognitive functions in ataxia with oculomotor apraxia type 2. Front Neurol 2012;10;3:125.

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