Ataxia with oculomotor apraxia type 1 in Southern Italy

Late onset and variable phenotype

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Abstract—Ataxia with oculomotor apraxia type 1 (AOA1) is an autosomal recessive disorder characterized by early-onset cerebellar ataxia, oculomotor apraxia, and peripheral neuropathy. The causative gene (*APTX*) has been recently identified in Portuguese and Japanese kindreds. Three patients with AOA1 were identified in an APTX mutation screening on 28 Southern Italian patients with progressive ataxia and peripheral neuropathy. A novel homozygous missense mutation (H201Q) was found in one patient and a Japanese missense mutation (P206L) in two. AOA1 clinical heterogeneity and onset later than previously described are shown.

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Ataxia with oculomotor apraxia type 1 (AOA1; MIM 208920) is the most frequent cause of autosomal recessive ataxia in Japan and second to Friedreich ataxia (FRDA) in Portugal.[1] It is a neurodegenerative disorder characterized by early-onset, progressive ataxia, peripheral neuropathy, and later oculomotor apraxia. The gene responsible for AOA1 (*APTX*) is organized into seven exons and maps to chromosome 9q13, spanning 17 kbp of genomic DNA. The encoded protein, aprataxin, has been involved in DNA single-strand break repair, as it shares similarity with the amino terminus of the polynucleotide kinase 3'-phosphatase and the histidine triad (HIT) proteins.[2] To date, several missense, nonsense, and frameshift mutations have been identified in Europe and Japan.[2-6]

We report clinical and molecular findings of three Southern Italian patients with mutations in the *APTX* gene.

Patients and methods. *Clinical study.* Twenty-eight index cases were selected among the ataxic patients followed at our department. The inclusion criteria were sporadic or autosomal recessive progressive cerebellar ataxia, onset within 35 years, clinical (decreased or absent ankle reflexes and decreased vibration sense) or neurophysiologic signs of peripheral neuropathy or both, and exclusion of GAA expansion or point mutation within the *X25* gene. Mean ± SD age at onset was 15 ± 13 years.

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Peripheral neurophysiologic examination was performed at median and posterior tibial nerves with needle electrodes.

Molecular study. Genomic DNA was extracted from peripheral blood samples after informed consent. Primer pairs were designed to screen for the seven coding exons of the *APTX* gene. Oligonucleotide primer pairs and PCR conditions are available on the *Neurology* Web site at www.neurology.org. PCR products were analyzed by denaturing high-performance liquid chromatography (DHPLC). DHPLC was performed on a WAVE Nucleic Acid Fragment Analysis System HSM (Transgenomic, Crewe, UK). Patients with altered DHPLC elution profile were analyzed by direct sequencing. PCR products were purified from agarose gels by the Qiagen gel extraction kit and directly sequenced on an automated sequencer (ABI 3100; Applied Biosystems, Foster City, CA) using the ABI-Prism Big-Dye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems).

Results. *Case reports.* Patient 1 had disease onset at age 28 with gait imbalance and tendency to fall (table). The patient became wheelchair bound at age 34. Routine chemistry showed slight hypoalbuminemia (3.5 g/dL) and hypercholesterolemia (281 mg/dL). Peripheral nerve conduction studies performed elsewhere showed sensory motor axonal neuropathy, but quantitative data are not available. Brain MRI revealed cerebellar atrophy more marked in the vermis.

The parents of Patient 2 were first cousins. Onset of the disease was at age 29 with mild dysarthria followed by progressive gait imbalance at 32 years. At age 38, he needed support for walking. Fasciculations were observed at the lower limbs. Serum creatine kinase level was elevated (462 U/L; normal 0 to 190 U/L). Sensory action potentials (SAPs) were undetectable at wrist and internal malleolus. Motor conduction velocities (MCVs) were slightly decreased at median (50 m/s in the elbow–wrist

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Table *Clinical and molecular findings*

Finding	Patient no.		
	1	2	3
Parental consanguinity	No	Yes	No
Sex	F	M	M
Age at onset, y	28	29	8
Age at examination, y	34	45	18
Gait and limb ataxia	+++	++	+
Dysarthria	++	++	+
Nystagmus	+	+	−
Eyes–head lag	−	−	+
Tendon reflexes	−	−	−
Extensor plantar response	−	−	−
Muscle wasting	++	++	+
Impaired position/vibration sense	+	+	+
Choreiform movements	−	−	+
Scoliosis	−	−	+
Pes planus	+	−	+
Cognitive impairment	−	−	+
Aprataxin mutations	P206L/P206L	H201Q/H201Q	P206L/A198V

Presence and severity of features: (+) = mild; (++) = moderate; (+++) = severe; (−) = absent.

segment; lower limit 54 m/s) and moderately at posterior tibial nerves (35 m/s in the popliteal fossa–internal malleolus segment; lower limit 52 m/s). Brain MRI revealed moderate cerebellar atrophy and multiple supratentorial white matter hyperintensities (figure).

Patient 3 had onset at age 8 with progressive gait imbalance. Sensory conduction velocity was moderately decreased at the median (37 m/s in the digit III–wrist segment; lower limit 51 m/s) and at the posterior tibial nerves (30 m/s in popliteal fossa–internal malleolus segment; lower limit 38 m/s). SAP was slightly reduced at the wrist (5 μV; lower limit 6 μV) and normal at the internal malleolus (0.6 μV; lower limit 0.2 μV). MCV was slight decreased at median (48 m/s) and moderately at posterior tibial nerves (40 m/s) in the same segments explored in Patient 2. Sural nerve biopsy confirmed axonal neuropathy with rare onion bulbs. MRI revealed cerebellar atrophy more marked in the vermis. IQ score was in the lower limits (88). Wolff–Parkinson–White–like abnormalities were found at EKG.

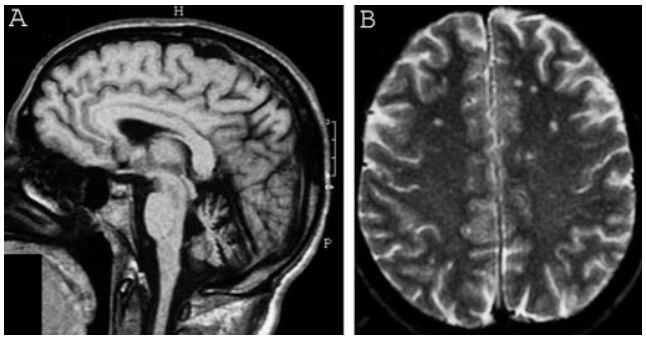

Figure. Patient 2. T1-weighted sagittal MRI showing cerebellar atrophy (A) and T2-weighted axial MRI showing white matter subcortical hyperintensities (B).

Molecular analysis. We identified a homozygous C-to-T transition at position 617 (we refer to the numbering starting at the first ATG codon of the long mRNA form), leading to the substitution of proline for leucine at position 206 of aprataxin (P206L). This mutation is one of the most frequent in Japan.[2,4,7] Sequencing of the *APTX* gene in Patient 2 showed a new homozygous missense mutation 603T→A, which results in the substitution of histidine for glutamine at amino acid residue 201 (H201Q). This substitution was not found in 200 Italian control chromosomes. Patient 3 had compound heterozygosity for P206L and 593C→T, which produces an alanine-to-valine replacement at residue 198 (A198V). Finally, one patient carried the substitution 431C→A (S144Y), a polymorphism with no detectable effect on the protein.[8]

Discussion. The relative frequency of AOA1 was 5.7% in a mixed European series of non-FRDA patients with progressive cerebellar ataxia,[5] 7.5% in a Portuguese series of patients with a possible AOA1 phenotype,[2] and 11.1% in the current series of patients with progressive non-FRDA and peripheral neuropathy.

The most frequent AOA1 phenotype comprises early-onset (2 to 18 years) cerebellar ataxia with cerebellar atrophy at MRI and areflexia with sensorimotor axonal neuropathy.[4-6] Choreic movements may be prominent at onset (79%) and decrease in the course of the disease.[5] The typical AOA1 oculomotor abnormality, frequent but not present in all patients (86%),[5] consists of normal ocular saccade initiation and increased duration with a succession of multiple hypometric saccades. Head reaches the target before the eyes as in congenital oculomotor apraxia, where initiation of saccades is impaired.[9] Thus, eyes–head lag may be a better definition.

Other clinical features include hypoalbuminemia and hypercholesterolemia in the late stage. Intelligence was normal in the Portuguese series,[1] whereas cognitive impairment was observed in the Japanese.[4] Recently, more detailed neuropsychological tests have shown in the European patients a subcortical syndrome probably due to disruption of frontocerebellar pathways.[5] No immunologic impairment has been reported. The patients become wheelchair bound after mean disease duration of 11.2 years.[5]

Patient 1 is homozygous for P206L, not previously described in the Caucasian population. P206L is the second commonest Japanese mutation, and it is constantly associated with hypoalbuminemia, as in Patient 1, and cognitive impairment, which is absent in Patient 1. Moreover, the onset (28 years) in this patient is later than previously described.

Patient 2 is homozygous for the novel H201Q mutation. The same codon is affected in the Japanese mutation H201R, suggesting a mutational hot spot. Japanese H201R patients show a typical phenotype with cognitive impairment.[3] Patient 2 shows a milder clinical presentation with late onset (29 years), no wheelchair use after 16 years of disease duration, and no cognitive impairment. The less severe presentation in Patient 2 suggests that glutamine substitution at position 201 is less deleterious than arginine for the protein function. MRI of this patient showed multiple supratentorial white matter hyperintensities in the absence of risk factors for cerebrovascular disease. White matter changes have not been described previously in AOA1 and may be coincidental. Presence of fasciculations suggests loss of motor neurons. This may be of interest as mutations in the gene responsible for AOA2, senataxin, may also cause juvenile ALS.[10]

Patient 3 is a compound heterozygote for A198V/P206L. A198V has been identified in a homozygous state in one Caucasian patient with persistent and severe chorea.[5] Patient 3 had persistence of choreic movements, suggesting that a single A198V dose is sufficient to cause this feature.

All the mutations (A198V, H201Q, P206L) are localized in exon 5 and probably alter the function of aprataxin, leading to changes in the HIT domain and in the secondary structure.

Late onset in Patients 1 and 2 and presence of fasciculations in Patient 2 suggest a wider clinical presentation and that AOA1 diagnosis should be also considered in ataxic patients with neuropathy and onset later than 20 years.

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