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Cerebellar ataxia with oculomotor apraxia type 1: clinical and genetic studies

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Summary

Ataxia with ocular motor apraxia type 1 (AOA1) is an autosomal recessive cerebellar ataxia (ARCA) associated with oculomotor apraxia, hypoalbuminaemia and hypercholesterolaemia. The gene *APTX*, which encodes aprataxin, has been identified recently. We studied a large series of 158 families with non-Friedreich progressive ARCA. We identified 14 patients (nine families) with five different missense or truncating mutations in the aprataxin gene (W279X, A198V, D267G, W279R, IVS5+1), four of which were new. We determined the relative frequency of AOA1 which is 5%. Mutation carriers underwent detailed neurological, neuropsychological, electrophysiological, oculographic and biological examinations, as well as brain imaging. The mean age at onset was 6.8 ± 4.8 years (range 2–18 years). Cerebellar ataxia with cerebellar atrophy on MRI and severe axonal sensorimotor neuropathy were present in all patients. In contrast, oculomotor apraxia (86%), hypoalbuminaemia (83%) and hypercholesterolaemia (75%) were variable. Choreic movements were frequent at onset (79%), but disappeared in the course of the disease in most cases. However, a remarkably severe and persistent choreic phenotype was associated with one of the mutations (A198V). Cognitive impairment was always present. Ocular saccade initiation was normal, but their duration was increased by the succession of multiple hypometric saccades that could clinically be confused with 'slow saccades'. We emphasize the phenotypic variability over the course of the disease. Cerebellar ataxia and/or chorea predominate at onset, but later on they are often partially masked by severe neuropathy, which is the most typical symptom in young adults. The presence of chorea, sensorimotor neuropathy, oculomotor anomalies, biological abnormalities, cerebellar atrophy on MRI and absence of the Babinski sign can help to distinguish AOA1 from Friedreich's ataxia on a clinical basis. The frequency of chorea at onset suggests that this diagnosis should also be considered in children with chorea who do not carry the *IT15* mutation responsible for Huntington's disease.

Keywords: AOA1; cerebellar ataxia; oculomotor apraxia; *APTX* gene; Friedreich's ataxia

Abbreviations: ARCA = autosomal recessive cerebellar ataxia; A–T = ataxia–telangiectasia; AOA = autosomal recessive cerebellar ataxias with oculomotor apraxia; AOA1 = ataxia with oculomotor apraxia type 1; AOA2 = ataxia with oculomotor apraxia type 2; *APTX* = gene encoding aprataxin; CMPA = compound muscle action potential; CVLT = California Verbal Learning Test; ECD-SPECT = 99mTc technetium-ethyl cysteinate dimmer single-photon emission computed tomography; HIT = histidine triad; HSMN = hereditary sensorimotor neuropathy; MADRS = Montgomery and Asberg Depression Rating Scale; MDRS = Mattis Dementia Rating Scale; MMSE = Mini-Mental Status Examination; OMA = oculomotor apraxia; PNKP = polynucleotide kinase-3′-phosphatase; SCA = spinocerebellar ataxia; SCAN = spinocerebellar ataxia with sensorimotor neuropathy; VOR = vestibulo-ocular reflex; WCST = Wisconsin Card Sorting Test

Introduction

Autosomal recessive cerebellar ataxias (ARCA) are a heterogeneous group of diseases. They include Friedreich's ataxia that accounts for ~30% of ARCA in the Caucasian population, as well as rarer disorders such as ataxia with vitamin E deficiency, autosomal recessive spastic ataxia of Charlevoix–Saguenay, infantile early-onset spinocerebellar ataxia and ataxia–telangiectasia (A–T) (Di Donato *et al*., 2001). Recently, a subgroup of autosomal recessive cerebellar ataxias associated with oculomotor apraxia (AOA) has been distinguished. This group includes at least two different genetic entities: ataxia with oculomotor apraxia type 1 (AOA1, also called early-onset ataxia with ocular motor apraxia and hypoalbuminaemia) and ataxia with ocular apraxia type 2 (AOA2).

AOA1 was initially described in Japanese families (Inoue *et al*., 1971; Aicardi *et al*., 1988; Uekawa *et al*., 1992; Kubota *et al*., 1995; Fukuhara *et al*., 1995; Hanihara *et al*., 1995; Sekijima *et al*., 1998; Tachi *et al*., 2000). The phenotype is characterized by early-onset cerebellar ataxia, oculomotor apraxia, neuropathy and mental retardation in most families. Hypoalbuminaemia and hypercholesterolaemia are often associated. A similar phenotype was described in several Portuguese families (Barbot *et al*., 2001) that enabled mapping of the locus designated AOA1 to chromosome 9p13 (Moreira *et al*., 2001*a*), followed by identification of mutations in the *APTX* gene in both Japanese and Portuguese families (Moreira *et al*., 2001*b*; Date *et al*., 2001). The *APTX* gene encodes aprataxin, a histidine-triad (HIT) protein the function of which is still unknown. However, aprataxin has a zinc-finger motif and a PANT (PNKP-aprataxin amino-terminal) domain sharing some homology with polynucleotide kinase-3′-phosphatase (PNKP), which suggests it could have a role in single-strand DNA break repair. All mutations identified so far are localized in exons 5, 6 and 7 which encode the HIT domain of the protein (Moreira *et al*., 2001*b*). The protein is widely expressed. In the nervous system it has been found in cerebellum, basal ganglia, cerebral cortex and spinal cord. Severe loss of Purkinje cells, degeneration of the posterior columns, spinocerebellar tracts and anterior horn cells of the spinal cord were observed post-mortem in one patient (Sekijima *et al*., 1998). The AOA2 locus was localized to chromosome 9q34 in Japanese and Pakistani families with a clinical phenotype resembling AOA1, but with elevated alpha-foetoprotein levels (Bomont *et al*., 2000; Nemeth *et al*., 2000). The defective gene has not yet been identified. In addition, a mutation in the *TDP1* gene encoding a topoisomerase–DNA resolvase was found recently to cause a similar phenotype in a Saudi Arabian family. The patients had autosomal recessive cerebellar ataxia, sensorimotor neuropathy (SCAN1), hypercholesterolaemia and hypoalbuminaemia, but no oculomotor apraxia (Takashima *et al*., 2002).

The relative frequencies, mutational spectrum and phenotypic characteristics of AOA1, AOA2 and SCAN1 have not yet been studied in detail. To evaluate the relative frequency of AOA1, and to provide an accurate description of the phenotype, we have screened a series of 227 patients with cerebellar ataxia. We identified 14 patients from nine families with AOA1, and present the results of a clinical, neuropsychological, oculographic and brain imaging study on this cohort, the largest series of such patients analysed to date.

Methods and patients

Recruitment of families and molecular genetics

A series of 158 families (227 patients) with progressive cerebellar ataxia including 75 multiplex families with ARCA (144 patients) and 83 patients without family history were selected after exclusion of Friedreich's ataxia by molecular analysis (absence of a GAA expansion in the first intron of the frataxin gene). All index cases gave written informed consent for the genetic study. They were mostly of French origin (73%). Clinical data, albumin and cholesterol levels were collected for all patients. In a subgroup of 48 families with cerebellar ataxia associated with either oculomotor apraxia and/or hypoalbuminaemia and/or hypercholesterolaemia, the *APTX* gene was analysed by sequencing exons 5, 6 and 7 as described previously (Moreira *et al*., 2001*b*).

Approval for the genetic study was given by the Ethics Committee of the CCPPRB Pitié-Salpêtrière.

Phenotypic characterization

All AOA1 patients underwent neurological examinations. Motor disability was assessed by a seven-stage functional scale: 0, normal; 1, mild modifications at examination; 2, mild functional disability, able to walk and run; 3, walking

without help <500 m, unable to run; 4, unilateral help to walk; 5, bilateral help to walk; 6, wheelchair-bound; 7, bedridden.

Oculomotor and electro-oculographic examination: definitions and tests

Oculomotor apraxia

Oculomotor apraxia (OMA) is a rare oculomotor disturbance that was initially defined by Cogan (1953) as the inability to initiate horizontal saccades in the head-fixed condition. Head rotation is usually necessary to initiate gaze shifts. The oculographic pattern is characterized by increased latencies and decreased amplitude of horizontal saccades. In contrast, vertical saccades are reportedly normal (Cogan *et al*., 1953; Zee *et al*., 1977; Leigh and Zee, 1999). Although the oculomotor disturbance in AOA1 does not correspond exactly to the definition of oculomotor apraxia (Cogan *et al*., 1953; Leigh and Zee, 1999), we have chosen to keep this term which was used in the initial description of the disease (Barbot *et al*., 2001). Here, the term 'oculomotor apraxia' (OMA) refers to the inability to coordinate eyes–head movements when the head turns toward a lateral target; the head reaches the target before the eyes.

Bedside oculomotor examination

Eye movements were evaluated clinically in 12 patients. Fixation, gaze holding, pursuit, vertical and horizontal saccades (latency, velocity, amplitude), presence and nature of nystagmus, vestibulo-ocular reflex (VOR), cancellation of the VOR and synergic eyes–head movements in the head-free condition were assessed.

Electro-oculographic recordings

Electro-oculographic recordings were performed in six patients, including four with and two without clinical OMA. The subject's head was immobilized and eye movements were recorded in complete darkness by horizontal direct-current electro-oculography with two temporal electrodes. Visual cues were presented at a distance of 95 cm with light-emitting diodes embedded in a curved ramp. All quantitative results were compared with those of six age-matched controls (mean age: 31 $\pm$ 9 years). In the gap task, the central point was switched off 200 ms (gap) before a luminous lateral target appeared 25° to the right or to the left of the central fixation point. After 1 s, the lateral target was switched off and the central fixation point was switched on simultaneously. The subject was instructed to fixate the central point, then to look at the lateral target as soon as it appeared 25° randomly right or left and then to go back to the central point. Left and right saccade latencies were calculated for each subject by averaging 20 measurements in each direction. The accuracy of centrifugal and centripetal saccades was expressed as a gain (amplitude of the first saccade with respect to the position of the target). The mean saccade velocity was determined for saccades with amplitudes from 5° to 25° $\pm$ 2°. To study better the voluntary component of horizontal saccades, a no-gap task was performed in four patients, including two patients with and two without oculomotor apraxia. The central point was switched off and the lateral target was simultaneously switched on; we measured the latency of the saccades. To distinguish a pathological gaze-evoked nystagmus (inability to maintain an eccentric gaze characterized by a centripetal drift followed by a centrifugal corrective saccade) from a physiological end-gaze nystagmus, the patients were asked to fixate a target 25° from the centre for 1 s. To qualitatively evaluate the VOR, the patients were asked to fixate a central point during active and passive head rotation with a total amplitude of 40° and a peak velocity of 15°/s. Cancellation of the VOR was determined while the patient fixed a target rotating sinusoidally at the same time as the head at a peak velocity of 15°/s.

Neuropsychological tests

IQ was evaluated in 11 patients with the Raven 47 coloured progressive matrices (PM47) (Raven, 1988). In addition, a detailed neuropsychological study was performed in six patients with normal or subnormal IQ to evaluate cognitive efficiency, memory and executive functions. The patient scores were compared with scores of normal population. Global cognitive efficiency was evaluated by the Mini-Mental Status Examination (MMSE) (Folstein *et al*., 1975) and the Mattis Dementia Rating Scale (MDRS) (Mattis, 1988). Recent memory was assessed by the California Verbal Learning Test (CVLT) based on word list learning and recognition (French norms established by B. Deweer but not published). This test evaluates memory performance both quantitatively and qualitatively, perseverations, intrusions, sensitivity to interference, capacities to initiate semantic and serial clustering, consistency of recall and recognition (Delis *et al*., 1987). Executive functions were evaluated with the frontal score (Pillon *et al*., 1995) including the simplified version of the Wisconsin Card Sorting Test (WCST) (Nelson, 1976) and two 1-min verbal fluency tasks (words beginning with letter 'm' and names of animals) (Thuillard and Assal, 1991). Mood was evaluated with the Montgomery and Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979).

Brain imaging

MRI, including T1- and T2-weighted sequences in sagittal, coronal and transaxial sections, was performed in all patients. In addition, brain perfusion was evaluated in three patients (F1P1, F3P1, F3P2) by 99mTc technetium-ethyl cysteinate dimmer single photon emission computed tomography (ECD-SPECT).

Table 1 *Phenotypic characteristics of 14 patients with AOA1*

	Families/patients													
	F1/P1	F2/P1	F2/P2	F3/P1	F3/P2	F4/P1	F4/P2	F5/P1	F6/P1	F6/P2	F7/P1	F7/P2	F8/P1	F9/P1
Mutation	A198V A198V	W279R IVS5+1	W279R IVS5+1	W279X D267G	W279X D267G	W279X W279X	W279X W279X	W279X W279X	W279X W279X	W279X W279X	W279X W279X	W279X W279X	W279X W279X	W279X W279X
Age at onset (years)	2	4	4	15	18	6	6	3	4	5	12	4	7	5
Disease duration (years)	22	51	49	21	17	46	44	9	31	27	42	32	14	10
Duration until wheelchair use	19	na	na	11	8	20	15	7	5	5	na	13	7	na
Functional handicap	4	7	7	5	5	6	6	3	6	6	na	6	5	3
Prominent sign at onset	Ch	Ch	Ch	CA	Dy	CA	CA	CA	Ch	Ch	CA	CA	CA	CA, Ch
Prominent sign at examination	CA, Ch	CA, PNP	CA, PNP	CA, PNP	CA, PNP	CA, PNP	CA, PNP	CA	CA, PNP	CA, PNP	PNP	PNP	CA	CA
Cerebellar ataxia	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Ocular apraxia	+	+	+	0	0	+	+	+	+	+	+	+	+	+
Chorea	+++	(+)	(+)	0	+	(++)	(++)	(+)	+	+	0	0	++	+
Dystonia	F, H	0	0	0	H	0	0	F, H	F	0	0	0	H	0
Cognitive impairment	DS	MR	MR	DS	DS	na	na	MR	DS	DS	DS	DS	DS	na
Tendon reflexes	a	a	a	a	a	a	a	na	a	a	a	a	d	a
Motor deficit	+++	+++	+++	+++	+++	+++	+++	na	+++	+++	+++	+++	+	+
Distal amyotrophy	+++	+++	+++	++	++	+++	+++	na	+++	+++	+++	+++	+	+
Decreased superficial sensory	+	+	+	+	+	+	+	na	+	+	+	+	0	+
Decreased vibration sense	++	+++	+++	++	++	na	na	na	++	++	+++	+++	++	++
Pyramidal sign	0	0	0	0	0	0	0	na	0	0	0	0	0	0
Pes cavus	+	na	+	0	0	+	+	na	0	+	na	+	0	0
Scoliosis	+	0	+	+	0	0	0	na	0	0	na	+	+	+
Limb oedema	0	+	+	0	0	0	+	na	+	0	+	+	0	0
Cholesterol level	↑	↑	↑	N	↑	↑	↑	N	↑	↑	na	↑	N	na
Albuminaemia (g/l)	31.0	5.0	15.0	30.0	33.0	33.5	22.5	38.7	27.0	34.0	na	27.6	41.0	na
CK level	↑	na	na	↑	N	↑	↑	na	↑	N	na	na	N	na

0 = Absent; + = present; ++ = moderate; +++ = severe; () = symptom disappearing with the course of the disease; ↑ = elevated level; a = abolished; CA = cerebellar ataxia; Ch = chorea; CK = creatine kinase; d = diminished; DS = dysexecutive syndrome; Dy = dystonia; F = face; F/P = family/patient; H = hand; MR = mental retardation; N = normal; na = not available; PNP = polyneuropathy; S = sensory; SM = sensorimotor. Normal values: total cholesterol <2 g/l; albumin level >38 g/l.

Biological investigations

In addition to albumin, protein electrophoresis, low density lipoprotein, high density lipoprotein and total cholesterol, triglycerides and alpha-foetoprotein were measured in 12 patients. Apolipoproteins A1 and B were measured in four patients.

Other investigations

Motor and sensory nerve conductions were carried out in the upper and lower extremities in 13 patients, as well as sensory and motor evoked potentials. Twelve patients underwent audiograms, brainstem auditory evoked potentials and ophthalmological examinations including fundoscopy, evoked visual potentials, visual field, electroretinograms. Sural nerve biopsy was performed for two patients (F6P2 and F7P2).

Results

Molecular analysis

Fourteen patients (three women, 11 men) with mutations in the aprataxin gene were identified. Ten patients were from five multiplex families; four had no family history of cerebellar ataxia (Table 1). Seven families were of French origin, one was Italian (family F7) and one Algerian (family F9). Five mutations, four of which were new (A198V, D267G, W279R, IVS5+1), were identified in exons 5 and 6 of the *APTX* gene in the nine families. All patients were either homozygous or compound heterozygous for the *APTX* mutations. As in the previously reported Portuguese families (Moreira *et al*., 2001*b*), the most frequent mutation was the 837G→A mutation (exon 6) leading to the W279X nonsense mutation, and a protein truncated at amino acid 279. Six families were homozygous for this mutation. In family 1, a homozygous 593C→T mutation was identified in exon 5, that led to the A198V missense variation in a highly conserved region of the protein. Compound heterozygous mutations were identified in two families (W279R/IVS5+1 and W279X/D267G). The 770+1–G→A mutation (IVS5+1) of the donor splice site of exon 5 should result in the deletion of exon 5. The absence of the A198V, W279R and D267G mutations was confirmed in 130 Caucasian controls.

Case reports

The two following case-reports are presented in detail to illustrate the phenotypic variability of AOA1.

Case report 1 (patient F7P2)

This 38-year-old man was investigated at age 32 years. He presented a history of foot deformities and staggering gait with frequent fallings at age 4 years. The disease was slowly progressive and he was unable to walk unaided at age 10 years. At age 19 years, he had loss of hand skilfulness, distal motor deficit and atrophy, truncal titubation, dysarthria and was confined to a wheelchair. Upright stance became impossible at age 32 years. The most prominent symptom at age 32 years was a severe 'Charcot–Marie–Tooth-like' sensorimotor peripheral neuropathy with generalized areflexia, a severe distal motor deficit, atrophy and deformities of hands and feet (*pes cavus*). Vibration sense was abolished, but superficial sensory sense was less severely affected. Cerebellar ataxia, hypotonia and dysarthria were evident. Eye movements were abnormal with OMA and saccadic pursuit. Electrophysiological studies confirmed severe axonal sensorimotor neuropathy. Nerve conduction studies showed absent median and sural sensory action potentials, and non-recordable compound muscle action potentials (CMPAs) evoked by distal stimulation of the ulnar, peroneal and tibial nerves. The median nerve was of low amplitude (4 mV, normal < 5), with a reduced conduction velocity between elbow and wrist (39 m/s, normal > 50). The sympathetic skin response was normally evoked in the hand. Histological examination of the sural nerve biopsy revealed severe loss of small and large myelinated fibres, but preservation of the unmyelinated nerve fibres (Fig. 1). Brain MRI showed severe cerebellar atrophy. Biological investigations revealed hypoalbuminaemia and hypercholesterolaemia. The patient's brother had a similar phenotype. The diagnosis of hereditary sensorimotor neuropathy (HSMN) was suspected. Mutations in the *PMP22* (peripheral myelin protein 22), *Cx32* (connexin-32) and *FRDA* (Friedreich's ataxia) genes were excluded by molecular analyses. A homozygous 837G→A base change leading to a W279X truncating mutation was identified in exon 6 of the *APTX* gene.

Case report 2 (patient F1P1)

This 24-year-old man had no family history of cerebellar ataxia. He was unsteady and had had diffuse choreic movements since the age of 2 years. The diagnosis of juvenile Huntington's disease was suspected. When he was 9 years old, he developed cerebellar ataxia and ocular abnormalities, but chorea was still predominant. Choreic movements partially decreased with neuroleptic drugs. He became confined to a wheelchair at the age of 21 years. At 24 years, examination showed severe disability with severe choreic movements, volitional dyskinesias of the limbs, hypotonia, dysarthric speech and cerebellar signs. Severe pharyngolaryngeal dyskinesias were responsible for swallowing difficulties. He had *pes cavus*, abolition of tendon reflexes and a severe distal motor deficit with amyotrophy of the feet and hands. Oculomotor examination revealed bilateral gaze-evoked nystagmus and abnormal saccadic pursuit. Horizontal and vertical saccades were hypometric. The duration of horizontal saccades was remarkably prolonged. The VOR was normally released, but VOR cancellation was altered. Severe oculocephalic dysynergy was observed when the patient was asked to look toward a lateral target with both

eyes and head movements. The head first turned toward the target, whereas the eyes moved contralaterally before slowly moving toward the target (Fig. 2). Biological investigations revealed hypercholesterolaemia and hypoalbuminaemia. Brain MRI showed severe cerebellar atrophy with vermian predominance associated with moderate brainstem atrophy. There were no trinucleotide repeat expansions in the *IT15* (Huntington's disease), *JPH-3* (junctophilin-3) and *FRDA* genes, but a homozygous 593C→T mutation, leading to an A198V substitution in the protein, was detected in exon 5 of the *APTX* gene.

Clinical characteristics

The clinical data of the 14 AOA1 patients are summarized in Tables 1 and 2. Mean age at onset was 6.8 ± 4.8 years (range 2–18) and mean disease duration 29.8 ± 14.8 years (range 9–51). The mean disease duration before confinement to wheelchair was 11.2 ± 5.7 years (range 5–20, mean age: 18.4 years). The predominant sign at onset was gait ataxia in eight patients (57%) and chorea or dystonia in seven (50%). OMA was variable (86%) with a mean delay after onset of 8.7 years (range 4–16). Interestingly, chorea was noticed at onset in 79% of cases, but persisted at the time of examination in only 43%. Thus, chorea spontaneously disappeared with the course of the disease in five patients, after a mean disease duration of 14.8 years. Severe disabling dyskinesias triggered by movements were observed in 29% of patients. Neuropathy became clinically evident in early adulthood (100%), leading to rapid and severe disability. At examination there were decreased reflexes or generalized areflexia (100%), a severe distal motor deficit (85%), severe atrophy (85%) with hand and foot deformities, impaired vibration sense (100%) with less severe superficial sensory loss (92%). Fasciculations

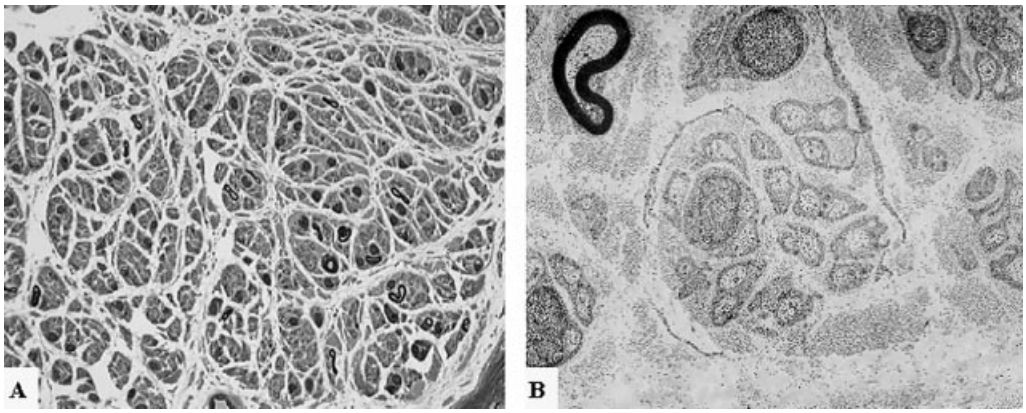

Fig. 1 Nerve histology in patient F7P2. (**A**) Light microscopy analysis of a sural nerve biopsy from patient F7P2. A 1-μm-thick section of the plastic-embedded specimen of a sural nerve biopsy specimen. Note the conspicuous reduction in the density of myelinated fibres. Thionine blue staining. Original magnification: ×630. (**B**) Electron micrograph of the sural nerve biopsy of patient F7P2. Besides the loss of myelinated nerve fibre this photograph shows the preservation of unmyelinated nerve fibres. Uranyl acetate and lead citrate staining. Original magnification: ×5000.

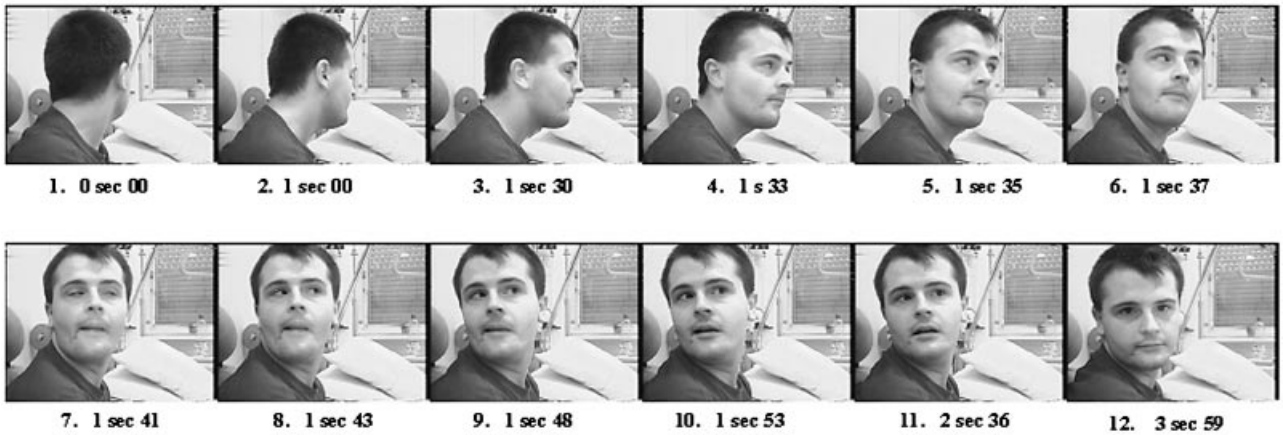

Fig. 2 Eyes–head dissociation in head-free condition in patient F1P1 with AOA1. Dissociation of eyes–head movements when looking toward a lateral target in the head-free condition (patient F1P1). A lateral head movement precedes the eye movements. The head first overshoots the lateral target (images 9 and 10), then returns to the target (image 12). Synkinetic blinking (images 3 and 7) is a strategy to avoid fixing images during eye rotation and to compensate for altered VOR cancellation.

Table 2 *Frequency of symptoms in 14 AOA1 patients*

Symptoms	Frequency*
Sensorimotor neuropathy	100 (13)
Cerebellar ataxia	100 (14)
Deep sensory loss	90(11)
Oculomotor characteristics	
Oculomotor apraxia	86 (14)
Gaze-evoked nystagmus	100 (14)
Fixation instability	100 (14)
Chorea	79 (14)
Dystonia	39 (14)
Cognitive impairment	100 (11)
Mental retardation	27
Dysexecutive syndrome	73
Pes cavus	55 (11)
Scoliosis	50 (12)
Limb oedema	46 (13)
Optic atrophy	17 (12)
Cerebellar atrophy on MRI	100 (14)
Hypoalbuminaemia	83 (12)
Hypercholesterolaemia	75 (12)

*The percentage value of the frequency is evaluated among the fraction of patients analysed per symptom and noted in parentheses.

were noted in two patients. Limb oedema was noted in 46% of patients, all of whom had long disease duration (>30 years) and low serum albumin levels (<30 g/l). Electrophysiological studies in 13 patients revealed unrecordable or severely decreased amplitudes of sensory and motor potentials, and mild to moderately decreased nerve conduction velocities. A loss of myelinated fibres without degeneration–regeneration or onion bulb formations was observed on histological examination in patients F6P2 and F7P2 (Fig. 1). The lesions predominantly affected the large myelinated fibres in the first patient, whereas all types of myelinated fibres (small and large) were affected in the second case. These features are consistent with severe axonal sensorimotor neuropathy.

Oculomotor characteristics: bedside oculomotor examination

Clinical examination revealed fixation instability or square-wave jerks, saccadic pursuit and gaze-evoked nystagmus in all patients. OMA, as defined above, was noted in 86% of patients. In addition to the eyes reaching the target after the head, synkinetic blinking to compensate for the lack of VOR

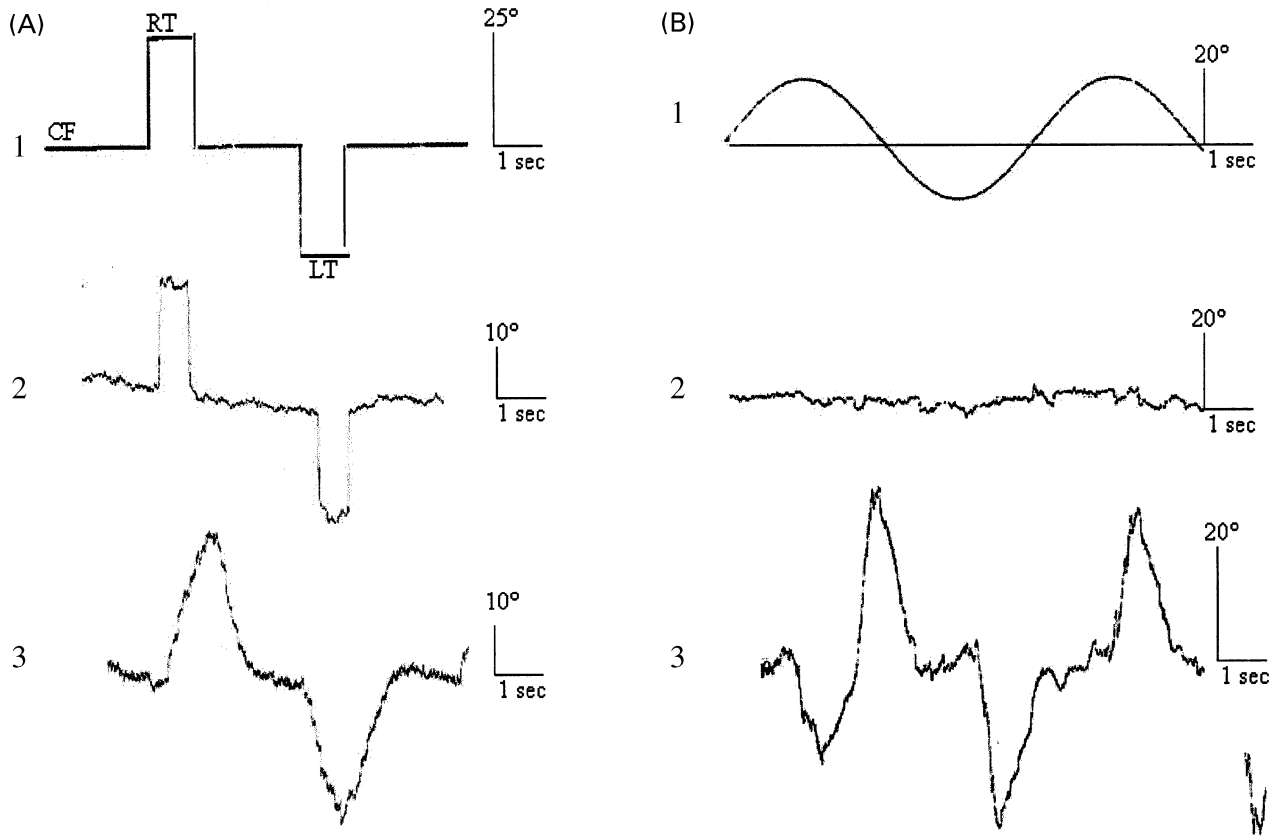

Fig. 3 Oculographic recordings in AOA1 patient F8P1 and control. Horizontal saccades in a gap task. (**A**) Visually guided saccade task: 1, schematic representation of the task (CF, central fixation; RT, right target; LT, left target); 2, performance of a control subject; 3, performance of the AOA1 patient in which the global duration of the saccade is prolonged stepwise, with multiple successive 5° saccades. (**B**) VOR cancellation task: 1, schematic representation of the task (the patient is asked to follow a target moving sinusoidally at the same time as the head) (R, right; L, left); 2, normal VOR cancellation in a control subject; 3, altered VOR cancellation in the AOA1 patient.

Table 3 *Results of neuropsychological testing in six AOA1 patients without mental retardation*

	Family/patients						Mean score
	F1/P1	F2/P1	F2/P2	F6/P1	F6/P2	F8/P1	
Age at evaluation (years)	24	36	35	35	32	21	30.5 ± 6.4
Education (years)	9	12	14	7	5	12	9.8 ± 3.4
Global IQ (PM 47)	(+)	0	0	0	0	(+)	0
MMSE	(+)	0	0	+	+	+	+
MDRS	+	(+)	+	+*	+*	+	+
Initiation	+	(+)	(+)	+*	+*	+	+
CVLT							
Monday list – total	+	+	0	+	+	(+)	+
Short delay free recall	(+)	(+)	0	(+)	(+)	0	(+)
Short delay cued recall	+	(+)	(+)	(+)	(+)	(+)	(+)
Long delay free recall	+	0	0	(+)	0	(+)	(+)
Long delay cued recall	+	0	0	(+)	(+)	+	(+)
Correct recognitions	+	+	0	0	0	(+)	0
Intrusions	0	0	0	0	0	0	0
Perseverations	0	0	+	0	0	0	(+)
Frontal score (/60)	+*	(+)	+	+*	+*	(+)	+
Fluency							
Phonemic (M)	+	(+)	(+)	(+)	+	(+)	(+)
Category	+	0	0	+	+	(+)	(+)
WCST							
Correct criteria	+	0	+	0	+	0	+

MDRS = Mattis Dementia Rating Scale; MMSE = Mini Mental Status Examination; CVLT = California Verbal Learning Test; WCST = Wisconsin Card Sorting Test; 0 = normal score, (+) = the score differs by 1 standard deviation from the mean in an age-matched population, + = abnormal score, which differs by 2 standard deviations from the mean age-matched population. *All subtests were not evaluated because of motor disability.

cancellation was observed. Horizontal and vertical saccades were hypometric.

Electro-oculographic observations (Fig. 3)

In one patient with OMA, saccade abnormalities and attentional deficit were so severe that saccade latencies and velocities could not be assessed. He was unable to reach the first target before the next target appeared. Three other patients with OMA had normal horizontal saccades latencies, when recorded, in the gap task (mean right saccade latency: 196 ± 42 ms versus 185 ± 31 ms in controls; mean left saccade latency: 188 ± 54 ms versus 164 ± 32 in controls) and in the no-gap task (mean right saccade latency: 245±34 ms versus 227 ± 41 ms in controls; mean left saccade latency: 250 ± 44 ms versus 220 ± 37 in controls), reflecting correct initiation of saccades. The saccades were overall very hypometric, with a decreased mean gain in amplitude (centrifugal: 0.58 ± 0.4 versus 0.99 ± 0.04 in controls; centripetal: 0.55 ± 0.2 versus 0.97 ± 0.04 in controls). Furthermore, saccades were broken into multiple successive saccades with a mean amplitude of ~5–15° that gave a step-like appearance. When observed at the bedside, they looked like slow saccades, although the short saccades were normal (e.g. the mean velocity of 5° saccades was 130°/s versus 153 ± 50°/s in controls). The VOR was normally released, whereas VOR cancellation was lost. Square-waves during central fixation and gaze-evoked nystagmus were observed in all patients. Because of loss of frontal inhibition, the percentage of errors increased in the anti-saccade task (38.1 ± 30% versus 4.3 ± 7.6% in controls).

Neuropsychological test results

Mental retardation (MR) was evident in three patients (IQ value: 63–73). Six patients had normal IQ values, but neuropsychological testing revealed cognitive deficit characteristics of subcortical syndrome. A low score was noted at the MMSE in four patients (range 19–26), and pathological scores were obtained at the MDRS in nearly all the patients, due to a deficit in initiation subtest (Table 3). In the CVLT, the patients performed significantly less well than control subjects on learning the first list and tended to perform less well on free recall and cued recall, but without loss of information after a delay interval. Recognition score exhibited a tendency of lower performance. A single patient showed pathological perseverations. All patients had low frontal scores, and most patients had disturbed WCST with decreased ability to form concepts and reduced verbal fluency. These abnormalities were consistent with a subcortical syndrome in all patients. Patients do not show significant scores on the MADRS.

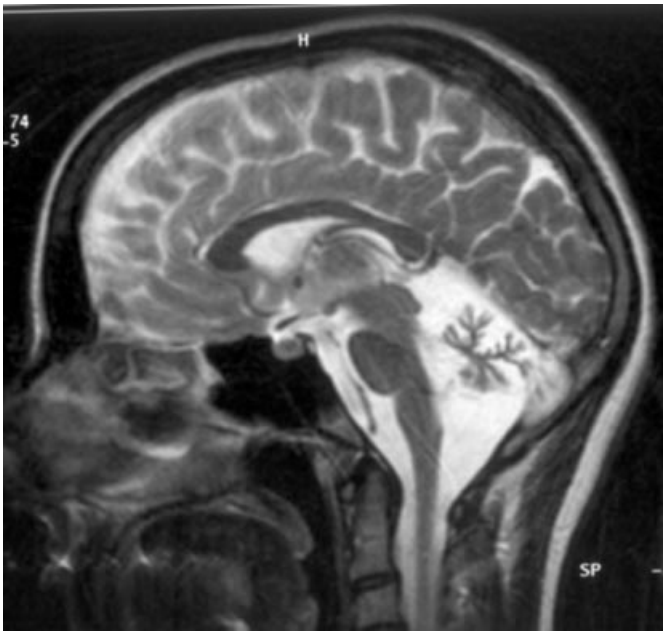

Fig. 4 Brain MRI of patient F8P1. Sagittal T2-weighted section showing severe cerebellar atrophy predominantly in the vermis (patient F8P1).

Brain imaging

Cerebellar atrophy was found on MRI in all patients, predominantly in the vermis in most of them (62%) (Fig. 4). Cerebellar hypoperfusion was seen in three patients who underwent brain ECD-SPECT. In one of these patients, moderate bilateral hypoperfusion in the caudate nuclei was also seen (Fig. 5).

Biological tests

Hypoalbuminaemia was present in 83% of patients (Table 1). Albumin levels were dramatically low in family F2. Hypercholesterolaemia was noted in 75% of patients, with elevated levels of low density lipoprotein cholesterol and low levels of high density lipoprotein cholesterol (n = 8). Apolipoprotein B was elevated and apolipoprotein A1 was decreased (n = 4). Disease duration was positively correlated with cholesterol (r = 0.72) and negatively correlated with albumin (r = –0.8) levels (Fig. 6). It is noteworthy that CPK (creatine phosphokinase) levels were 1.2–9 times the normal upper limit in 50% of the patients.

Other investigations

Fundoscopy revealed macular and retinal exudative lesions in 50% of the patients. Optic atrophy was noted in two patients (17%). In the four other patients, fundoscopy, visual evoked potentials and electroretinogram were normal (33%). In contrast to Friedreich's ataxia, no hearing loss could be evidenced and brainstem auditory evoked potentials and audiogram were normal in 11 patients.

Discussion

We have described here the largest series of patients with molecularly proven AOA1, recruited from among a large series of 227 patients with progressive cerebellar ataxia after exclusion of Friedreich's ataxia. The relative frequency of AOA1 was 5.7% [95% CI (confidence interval): 0.0264–0.1054] in families with progressive cerebellar ataxia, but without Friedreich's ataxia (7% of ARCA, 5% of ataxias without family histories). However, if only patients with cerebellar ataxia with onset before the age of 25 years are considered, the frequency reaches 9.1%. This value is lower than the 21% reported in a Portuguese population-based study (Barbot *et al*., 2001) which was performed before the identification of the *APTX* gene. Mutations were subsequently found in less than half of the families, reducing the frequency to 7.5% (Barbot *et al*., 2001; Moreira *et al*., 2001*a*, *b*). AOA1 should therefore be considered as a possible diagnosis in all patients with early-onset cerebellar ataxia with or without familial histories, after exclusion of Friedreich's ataxia.

The most frequent AOA1 phenotype associates cerebellar ataxia with cerebellar atrophy visualized by MRI, chorea, axonal sensorimotor neuropathy and deep sensory loss as previously described (Shimazaki *et al*., 2002; Tranchant *et al*., 2003). OMA, which is the hallmark of the disease, is present in most (86%), but not all patients. Two distinct phenotypic stages can be distinguished: at onset cerebellar ataxia and chorea are the most consistent symptoms, whereas OMA and neuropathy are usually absent; later, the predominant symptom is severe disabling neuropathy. In several families (including one of ours), the severity of the distal motor deficit, atrophy and deformities suggested the diagnosis of hereditary sensory motor neuropathy (Uekawa *et al*., 1992; Fukuhara *et al*., 1995; Sekijima *et al*., 1998), which is consistent with the marked loss of small and large myelinated fibres on nerve biopsies. The clinical course is rapidly progressive, with a mean disease duration of 11.2 years (ranging from 5 to 20), before the patients become wheelchair-bound. Our results confirm that hypoalbuminaemia parallels disease duration after onset (Shimazaki *et al*., 2002), but we also demonstrate that cholesterol levels increase with time. We emphasize the need to repeat biological investigations since the abnormalities are variable and the values fluctuate. In addition, the profile of cholesterol and apolipoproteins suggests an increased risk for atheromatosis that should be prevented. Finally, the main clinical features distinguishing the 39 families who were selected for *APTX* gene screening, but did not have mutations were a later mean age at onset (16.8 years) and less frequent neuropathy (67%), cognitive impairment (26%), dystonia (16%) and chorea (11%) than in AOA1 families (Table 4).

The most frequent mutation (W279X) was the same as in Portuguese patients (Moreira *et al*., 2001*b*), but we identified four new mutations in our screen. Interestingly, the compound heterozygous mutation (W279X/D269G) observed in a single family (F3) was associated with a later age at onset (15

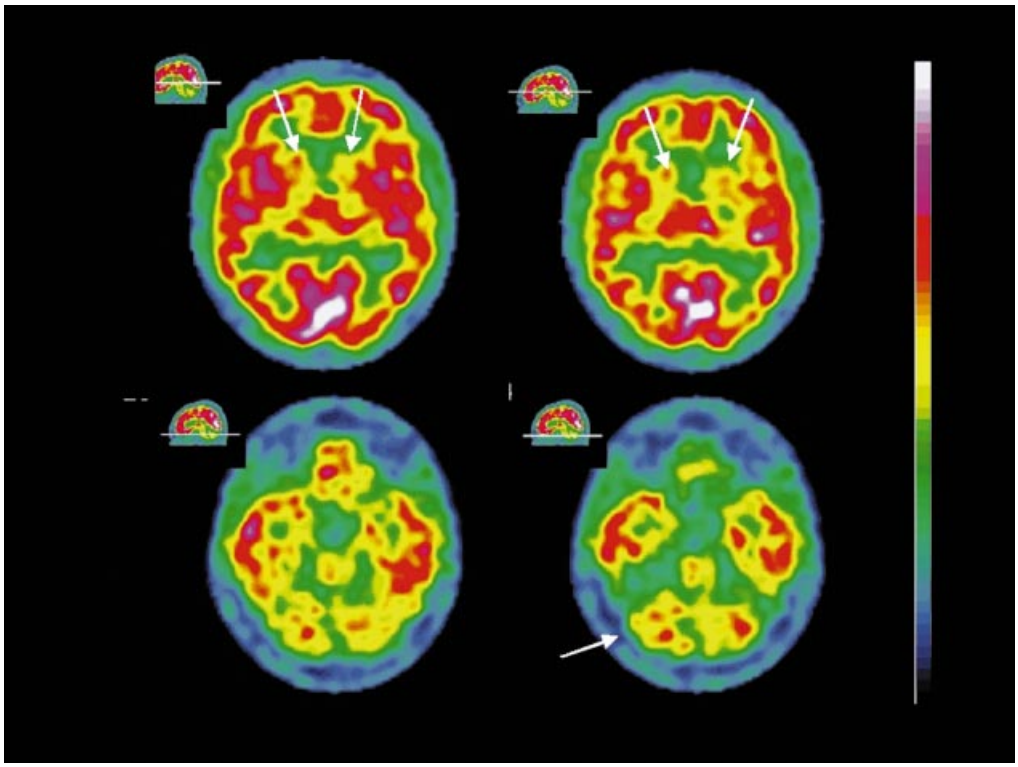

Fig. 5 Brain ECD-SPECT in patient F3P2. Arrows indicate cerebellar hypoperfusion in patient F3P2 (*below*) associated with moderate bilateral hypoperfusion in the caudate nuclei (*above*).

and 18 years) and the absence of OMA in both patients, suggesting that the D269G mutation leads only to a partial loss of aprataxin function. The homozygous missense mutation A198V was associated with predominant, severe and persistent chorea. No phenotype–genotype correlations could be established in this series between the different mutations and mental retardation and severity or the course of the disease. In addition, age at onset and disease progression varies among the eight patients with homozygous W279X nonsense mutation.

The oculomotor disturbances in AOA1 patients differ in two respects from ocular apraxia described in congenital oculomotor apraxia (Cogan, 1953): triggering of saccade is normal and vertical saccades are altered. Oculographic recordings in AOA1 patients reveal normal latencies (in both the gap and no-gap tasks), but a dramatic increase in the duration of horizontal saccades in the head-fixed condition mimics slow eye movements. In fact, the velocity of the saccades is almost normal, but they are broken into numerous small saccades ~5–15° in amplitude. This decreased gain in amplitude probably results from atrophy of the posterior vermis, known to be involved in the control of saccade accuracy in humans. Furthermore, VOR cancellation is altered, increasing the eyes–head movement dissociation in the head-free condition. Clinically, the oculomotor disturbances in AOA1 resemble those observed in spinocerebellar ataxia type 2 (SCA2), a form of autosomal dominant cerebellar ataxia (Rivaud-Pechoux *et al*., 1998), in which the appearance of gaze slowness and oculocephalic dissociation is caused by a decrease in saccade velocity. In addition to oculomotor abnormalities, fundoscopy showed macular and retinal lesions in most patients, and optic atrophy in two. These features of AOA1 had not been described previously.

Chorea is remarkably frequent in our series, leading to erroneous initial clinical diagnoses of juvenile Huntington's disease, Sydenham's chorea or hereditary benign chorea in five patients from three families. As in hereditary benign chorea (de Vries *et al*., 2000), the evolution is favourable with a progressive decrease in the choreic movements over time. Although no morphological abnormalities in the basal ganglia have been evidenced, caudate nucleus hypoperfusion was detected in a single patient. Since aprataxin is expressed in the caudate nuclei (Date *et al*., 2001), aprataxin mutations might be hypothesized to compromise the function of this brain structure. Our study establishes that cognitive changes are a consistent finding in AOA1. Mental retardation, however, was less frequent in our series than previously reported in Japanese families (Tachi *et al*., 2000; Shimazaki *et al*., 2002). Interestingly, all patients with normal IQ values showed memory impairment characterized by disturbed learning and retrieval information. These memory disturbances were associated with executive dysfunction exhibited by difficulties in initiation, conceptualization, reduced verbal fluency and low frontal scores. The cognitive profile is consistent with a subcortical syndrome that may result from

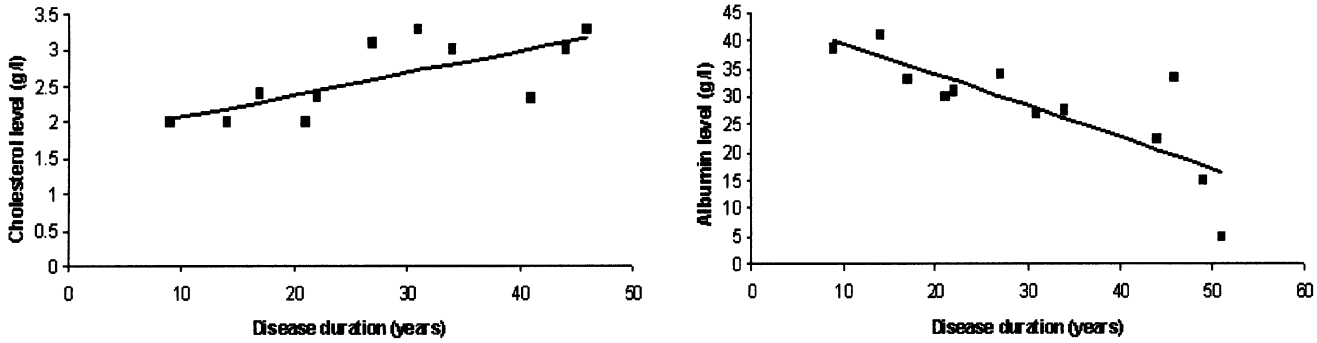

Fig. 6 Correlations between disease duration and blood levels of cholesterol (*left*) and albumin (*right*).

Table 4 *Differential diagnosis between Friedreich's ataxia and AOA1*

	Friedreich's ataxia*	AOA1†
Age at onset (years) (range)	16 (2–58)	6.9 (2–18)
Inheritance	AR	AR
Gene	*FRDA* (9q13)	*APTX* (9p13)
Relative frequency‡	30–40%	~5%
Cerebellar ataxia	+	+
Babinski sign	+	0
Cardiomyopathy	+	0
Oculomotor apraxia	0	+
Chorea	0	+
Neuropathy	Sensory	Sensory and motor
Hypercholesterolaemia	0	+
Hypoalbuminaemia	0	+
Severe cerebellar atrophy (MRI)	0	+

*From Dürr *et al*. (1996); †in our series; ‡in Europe.

disruption of the fronto-cerebellar pathways. The frequency of cognitive changes in our patients contrasts with previously reported Portuguese patients whose cognitive status was always considered normal (Barbot *et al*., 2001). This shows that detailed neuropsychological testing can detect the subtle neuropsychological deficits characteristic of AOA1.

Although the age at onset may be similar, the absence of oculo-conjunctival telangiectasias, chromosomal breakage with predisposition to cancer and infection help to distinguish AOA1 from A–T. Biological markers may also be useful, since the serum alpha-protein level is normal in AOA1, as well as cholesterol and albumin in A–T. In addition, we confirm that differential diagnosis between AOA1 and Friedreich's ataxia can easily be made on clinical grounds (Table 4). AOA1 patients do not have extensor plantar reflex, cardiomyopathy, and peripheral neuropathy is sensorimotor, but purely sensory in Friedreich's ataxia (Harding, 1981). Conversely, chorea and OMA are absent in Friedreich's ataxia as well as biological abnormalities (hypercholesterolaemia, hypoalbuminaemia) and early cerebellar atrophy on MRI (Dürr *et al*., 1996).

In conclusion, we would like to suggest that *APTX* mutations are looked for in autosomal recessive or isolated cases with progressive cerebellar ataxia after exclusion of Friedreich's ataxia, and when onset occurs before the age of 25 years. At onset, characteristic features such as oculomotor apraxia or biological abnormalities are often lacking, but the presence of choreic movements is highly suggestive of AOA1. Since the AOA1 phenotype at onset can resemble other choreic disorders, early-onset choreic patients without expansions in the *IT15* and *JPH3* genes (Stevanin *et al*., 2002) should also be tested for *APTX* mutations.

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