

# Recessive Ataxia With Ocular Apraxia

## Review of 22 Portuguese Patients

Clara Barbot, MD; Paula Coutinho, MD, PhD; Rui Chorão, MD; Carla Ferreira, MD; José Barros, MD; Isabel Fineza, MD; Karin Dias, MD; José P. Monteiro, MD, PhD; António Guimarães, MD; Pedro Mendonça, BSc; Maria do Céu Moreira, MSc; Jorge Sequeiros, MD, PhD

**Background:** The recessive ataxias are a heterogeneous group of neurodegenerative disorders characterized by cerebellar ataxia associated with a number of different neurologic, ophthalmologic, or general signs. They are often difficult to classify in clinical terms, except for Friedreich ataxia, ataxia-telangiectasia, and a relatively small group of rare conditions for which the molecular basis has already been defined.

**Objectives:** To study the clinical presentation and to define diagnostic criteria in a group of Portuguese patients with ataxia and ocular apraxia, an autosomal recessive form without the essential clinical and laboratory features of ataxia-telangiectasia.

**Patients and Methods:** We reviewed 22 patients in 11 kindreds, identified through a systematic survey of hereditary ataxias being conducted in Portugal.

**Results:** Age at onset ranged from 1 to 15 years, with a

mean of 4.7 years. The duration of symptoms at the time of last examination varied from 5 to 58 years. All patients presented with progressive cerebellar ataxia, the characteristic ocular apraxia, and a peripheral neuropathy. Associated neurologic signs included dystonia, scoliosis, and pes cavus. Magnetic resonance imaging was performed in 16 patients, all of whom showed cerebellar atrophy.

**Conclusions:** Ataxia with ocular apraxia may be more frequent than postulated before, and may be identified clinically using the following criteria: (1) autosomal recessive transmission; (2) early onset (for most patients in early childhood); (3) combination of cerebellar ataxia, ocular apraxia, and early areflexia, with later appearance of the full picture of peripheral neuropathy; (4) absence of mental retardation, telangiectasia, and immunodeficiency; and (5) the possibility of a long survival, although with severe motor handicap.

*Arch Neurol.* 2001;58:201-205

From the Department of Pediatric Neurology, Hospital Maria Pia (Dr Barbot), Department of Neurology, Hospital Santo António, (Drs Ferreira, Barros, and Monteiro), the Neuropathology Unit, Hospital Santo António (Dr Guimarães), and UniGENe, Instituto de Biologia Molecular e Celular, University of Porto (Drs Barbot, Coutinho, and Sequeiros; Mr Mendonça; and Ms Moreira), Porto; the Departments of Neurology, Hospital de São Sebastião, Santa Maria da Feira (Dr Coutinho), and Hospital de São Pedro, Vila Real (Dr Chorão); and Departments of Pediatric Neurology, Hospital Pediátrico, Coimbra (Dr Fineza), and Hospital de D Estefânia, Lisboa (Dr Dias), Portugal.

**O**CULAR APRAXIA, defined as the limitation of ocular movements on command dissociated from movements of pursuit, is a major clinical feature in 2 well-defined hereditary ataxias, spinocerebellar ataxia type 2 and ataxia-telangiectasia (A-T). In 1941, Louis-Barr<sup>1</sup> described A-T as an autosomal recessive cerebellar ataxia beginning in early childhood, associated with ocular apraxia, choreoathetosis, oculocutaneous telangiectasia, immune dysfunction, chromosomal instability, and hypersensitivity to x-rays, with a high incidence of respiratory infections and neoplasias; it was associated with chromosomal instability and DNA repair defects<sup>2</sup> and mapped to chromosome 11.<sup>3</sup> Spinocerebellar ataxia type 2 is an adult-onset, autosomal dominant, cerebellar ataxia, first reported in India by Wadia and Swami,<sup>4</sup> that has a large cluster in the Cuban province of Holguin.<sup>5</sup> The mu-

tation, a CAG repeat expansion in the short arm of chromosome 12, was identified in 1996.<sup>6</sup>

In 1988, Aicardi et al<sup>7</sup> reviewed 14 patients (including 6 previously described in Japan, Canada, and United Arab Emirates,<sup>8-12</sup>) with a neurologic picture similar

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to that of A-T, but without any of its extraneurologic features. This new form of recessive ataxia was considered rare, and few reports were published thereafter.<sup>13,14</sup> Through a systematic population survey of inherited ataxias we are performing in Portugal,<sup>15</sup> several new families with ataxia associated with ocular apraxia (AOA) have been identified. We decided therefore to study the clinical presentation of this peculiar disease and to define diagnostic criteria.

## PATIENTS AND METHODS

We studied 22 patients in 11 families of Portuguese origin. Most patients have been ascertained during a systematic, population-based survey of hereditary ataxias and spastic paraplegias that is being conducted in Portugal.<sup>15</sup> Initiated in 1993, the survey has now covered 4841444 inhabitants, approximately half of the Portuguese population. Other patients were referred by their assistant neurologists. All were examined by one of us (C.B.) in a health center or at home. Their parents and nonaffected siblings were also examined. Whenever possible, the proband from each family was hospitalized for further investigation, including cellular and humoral immunological studies and  $\alpha$ -fetoprotein (AFP) levels, electromyographic studies, and cranial magnetic resonance imaging (MRI). Five patients underwent a nerve biopsy.

## RESULTS

Our series includes 8 male and 14 female patients (sex ratio, 1:1.75). The age at last examination ranged from 9 to 60 years (mean age, 25.5 years), corresponding to a disease duration of 5 to 58 years (mean duration, 20.8 years).

### CLINICAL PRESENTATION

The main clinical features are summarized in **Table 1**.

#### Age at and Mode of Onset

The first manifestations, gait imbalance followed by dysarthria, were noticed between 1 and 16 years of age (mean age, 4.7 years). As illustrated in the **Figure**, 19 (86%) of the patients experienced onset of the disease before school age. There was no sex difference regarding the age at onset.

#### Cerebellar Ataxia

Ataxia was present in all 22 patients and was first defined by slowly progressive gait imbalance and dysarthria after initially normal motor development, followed by upper limb dysmetria, with mild intention tremor.

#### Ocular Findings

Ocular apraxia is the most striking feature in this disorder, and was present in all 22 patients. It was never the initial complaint, and was usually noticed a few years after the onset of gait ataxia. Patients appear not to fixate normally on objects. When asked to look to one side, they turn their head first, with eye contraversion, and then their eyes follow in several slow saccades to the same side with head thrusts. Ocular movements on command are

usually slightly limited, with the eyes stopping before reaching extreme positions. Eye and head movements have an ataxic component. Besides being slow, they are abrupt, dysmetric, and decomposed. These slow eye movements appear equally on lateral and vertical gaze, in the same way. When the patients are standing, turning their heads makes them lose their balance, and they tend to move the whole body around. When the head is immobilized, the movement of the eyes is impossible. Blinking is exaggerated in most patients. Pursuit movements remain normal during the first years after the appearance of ocular apraxia; then a progressive external ophthalmoplegia (beginning by upward gaze) is noticed (seen in 14 [64%] of 22 patients). Oculocephalic reflexes are spared until advanced stages of the disease.

#### Peripheral Neuropathy

All patients examined (with minimum disease duration of 5 years) had generalized areflexia. A few years later, distal muscular wasting and weakness appear, leading to tetraplegia with extremely short, atrophic hands and feet. Vibration and postural sense were impaired only in older patients with very long disease duration. Pain and light touch sensation were preserved.

#### Dystonia

There was a dystonic posturing of the upper extremities in 13 patients (59%). In 3 of these patients, 2 from the same family (family 9 in Table 1), dystonia associated with masklike faces appeared early in the disease, and was so relevant to the clinical presentation that those patients underwent the diagnostic procedures for extrapyramidal disorders. In the other 10 patients, dystonia was mild.

#### Other Signs

Pes cavus were present in 9 patients (41%) and scoliosis in 6 (27%). Three patients in the same kindred (family 10 in Table 1) had optic atrophy beginning late in life. No signs of extraneurologic involvement were evident, except for obesity in 4 patients. Despite a long evolution and extreme motor incapacity, there were no signs of mental retardation or deterioration in our patients.

#### Disability

Ataxia represented the main cause of disability in the first stages of the disease. Later, peripheral neuropathy dominated the clinical picture. Loss of the ability to walk independently happened after 7 to 10 years of evolution, with most patients being wheelchair bound by early adulthood.

#### Survival

Two patients died, one of a thalamic tumor at 11 years of age, the other at 53 years of age after long-standing disability and a disease duration of 52 years.

**Table 1. Summary of Clinical Features in 22 Patients With AOA\***

Patient No.	Family	Consanguinity	Sex	Age at Onset, y	Age at Last Examination, y	Disease Duration, y	PEO	Dystonia	Neuropathy	Pes Cavus	MRI/CT Findings	EMG Findings	Nerve Biopsy	Special Features
1	1	+	F	5	10	5	-	-	+	-	CA	N	ND	...
2	1	+	F	5	60	55	+	-	+	-	CA	PN	ND	...
3	1	+	F	15	55	40	+	-	+	-	ND	PN	ND	...
4	2	-	M	16	25	9	+	-	+	-	CA	PN	ND	...
5	3	+	F	6	21	15	-	-	+	-	CA	PN	ND	Obesity
6	4	-	F	2	21	19	+	+	+	-	ND	ND	ND	...
7	4	-	F	2	9	7	-	+	+	+	CA	PN	ND	...
8	4	-	M	2	20	18	+	+	+	+	CA	PN	PN	...
9	5	+	F	4	13	9	-	-	+	-	CA/BSA	ND	ND	...
10	5	+	F	4	11	7	-	+	+	-	ND	ND	ND	...
11	5	+	F	3	9	6	-	+	+	-	CA	ND	ND	...
12	5	+	M	5	10	5	-	+	+	-	CA/BSA	N	ND	...
13	6	-	F	10	16	6	+	+	+	-	CA/BSA	PN	PN	...
14	6	-	M	5	18	13	+	+	+	+	CA	PN	ND	...
15	7	-	F	5	14	9	+	+	+	+	CA	PN	ND	...
16	8	-	M	1	18	17	+	+	+	+	CA	ND	PN	...
17	9	-	M	3	21	18	+	+	+	+	CA	PN	PN	Obesity
18	9	-	F	2	23	21	+	+	+	-	CA/BSA	PN	PN	Obesity
19	10	+	F	1	50	49	+	-	+	-	ND	ND	ND	Optic atrophy
20	10	+	M	1	52	51	+	-	+	+	CA	PN	ND	Optic atrophy
21	10	+	M	1	59	58	+	-	+	+	ND	ND	ND	Optic atrophy
22	11	+	F	5	26	21	-	+	+	-	CA	PN	ND	Obesity

\*All patients had both ataxia and ocular apraxia. AOA indicates ataxia with ocular apraxia; PEO, progressive external ophthalmoplegia; MRI, magnetic resonance imaging; CT, computed tomographic scanning; EMG, electromyographic study; CA, cerebellar atrophy; N, normal; ND, not done; ellipses, no special features; PN, peripheral neuropathy; BSA, brainstem atrophy; N, normal; PN, peripheral neuropathy; BSA, brainstem atrophy; plus sign, positive; and minus sign, negative.

## LABORATORY INVESTIGATION

### Exclusion of A-T

Levels of AFP and immunoglobulins were normal in the 11 probands. In 4 patients studied, no cytogenetic abnormalities of chromosomes 7 and 14 were found.

### Exclusion of Friedreich Ataxia

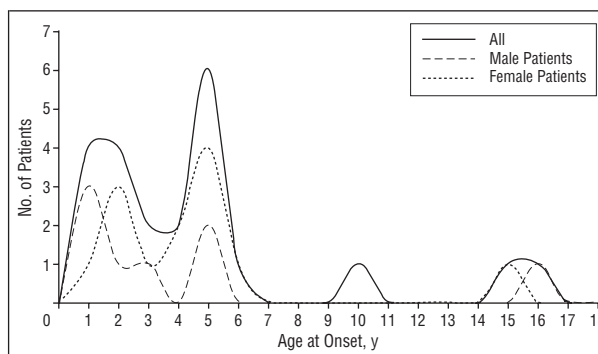
Nineteen patients from 10 families with AOA have undergone testing for GAA expansions at the gene for Friedreich ataxia. All of these patients had alleles of normal size.

### Neurophysiological Studies

Electromyographic studies were performed in 15 patients. An axonal neuropathy was found in 12; the other 2 patients with normal results underwent investigation at a very early stage of the disease.

### Nerve Biopsy

Nerve biopsies were performed in 5 patients (Table 2). In 4 of these (patients 8, 13, 16, and 18), the myelinated fiber density was reduced, due to the absence of large-diameter fibers. The histograms showed unimodal findings, with fiber diameters ranging from 2 to 10  $\mu\text{m}$  and a peak at 3- and 4- $\mu\text{m}$  fibers. The other patient (patient 17, the brother of patient 18) underwent nerve biopsy earlier in the disease course. The density of myelinated fibers was normal; the histo-



Age at onset in the 22 Portuguese patients with ataxia and ocular apraxia.

gram still showed bimodal results, but with 1 abnormally short peak at 10- $\mu\text{m}$  fibers. Degenerating myelinated fibers were present in patients 13, 17, and 18. No "onion bulbs," ie, regenerating clusters of fibers with abnormally thin myelin sheaths, were observed. Electron microscopic study of all cases did not disclose evidence of storage diseases. Three of these patients also underwent muscle biopsies. In patient 13 there was an evident small-group atrophy, and in patients 8 and 18, a severe large- and small-group neurogenic atrophy. There was no evidence of reinnervation of muscle fibers (ie, no type grouping).

### Neuroimaging

Seventeen patients showed evidence of cerebellar atrophy on MRI (n=16) or computed tomographic scan (n=1). In addition, 4 patients (with 5, 6, 9, and 21 years

**Table 2. Summary of Nerve and Muscle Biopsy Findings in Patients With AOA\***

Patient No.	Myelinated Fiber Density, No./mm <sup>2</sup>	Histogram (Range of Fiber Diameters, μm)	Degenerating Fibers	Neurogenic Muscular Atrophy
8	6610	Unimodal (2-7)	No	Yes
13	7520	Unimodal (2-10)	Yes	Yes
16	8030	Unimodal (2-9)	No	...
17	10 760	Bimodal (2-13)	Yes	...
18	6600	Unimodal (2-10)	Yes	Yes
Reference values†	9450-11 960	Bimodal (2-15)	NA	NA

\*AOA indicates ataxia with ocular apraxia; NA, not applicable; and ellipses, not examined.

†Includes 4 patients aged 3, 13, 14, and 16 years (control group for reference values).

of evolution) had atrophy of the brainstem. One of the oldest patients (with 55 years of evolution of the disease) had a spontaneous hyperintensity of the dentate nuclei on T2-weighted MRI.

### FAMILY STUDIES

In each family, all patients appeared in the same sibship, except for one kindred with a pseudodominant pattern of inheritance explained by successive consanguineous matings (family 1), and another in which patients appeared in 2 sibships (family 5). There was a history of consanguinity in 5 kindreds. Three patients, with no evidence of parental consanguinity, represented isolated cases.

The most relevant features of each family are summarized in Table 1. A homogeneous age at onset was verified in 9 families. As is often the case, the eldest affected member of the sibship tended to have a reportedly later onset, because of the family's awareness of the disease. All families also showed a complete homogeneity in the neurologic expression of the disease.

### GEOGRAPHIC DISTRIBUTION IN PORTUGAL

Most patients with AOA came from the northern and central regions of mainland Portugal, but there was no evidence of geographic clustering of the disease, even when considering their residence or the place of origin of the oldest known members of the family.

### COMMENT

Autosomal recessive AOA is a well-defined condition in clinical terms. The main key to the diagnosis is the presence of ocular apraxia. This feature nevertheless may be overlooked. In early phases of the disease, the examiner may not be familiar with it; in advanced cases, the external ophthalmoplegia can mask the ocular apraxia.

The differential diagnosis of AOA vs A-T, a multi-systemic disorder, is based on the absence of telangiectasia, immunodysfunction, cytogenetic abnormalities of chromosomes 7 and 14, and normal levels of AFP. This exclusively neurologic involvement, without the complications of infection, cancer, or premature aging, allows AOA patients a much longer survival.

Another important feature in our series of patients is the presence of an axonal peripheral neuropathy, with very early areflexia. This neuropathy dominates the clinical picture in the advanced phases of the disease and is the major cause of disability in these patients, who remain tetraplegic for several years, confined to a wheelchair, and with marked distal atrophies. Pathologically, this neuropathy is characterized by the absence of large-diameter fibers and preservation of the small-diameter fibers, without any evidence of regeneration. The motor neuropathy is also demonstrated by the neurogenic atrophy present in muscle biopsy findings.

Dystonia was present in 13 patients, although it is sometimes difficult in ataxic patients to be certain that the position (particularly of the hands) we are calling dystonia is not just extreme ataxia. One family initially underwent investigation for a progressive dystonia.

Cerebellar atrophy was a consistent finding in our patients; it was sometimes combined with brainstem atrophy. No correlation was found between the brainstem involvement and the disease duration. These MRI findings are one of the main features in the differential diagnosis of AOA vs Friedreich ataxia, along with the earlier onset in AOA.

The clinical picture of AOA is strikingly repetitive. Through our survey in Portugal, another group of recessive ataxias with peripheral neuropathy but without ocular apraxia has been detected. We wonder whether, when a molecular diagnosis is available, the spectrum of the disease will cover other clinical variants. Comparing the present series with the previous description by Aicardi et al,<sup>7</sup> we found a great constancy and prominence of the peripheral neuropathy and existence of cerebellar atrophy in all patients. Our data also gave an overview of the natural course of AOA that is in disagreement with the findings of Gascon et al,<sup>13</sup> who found a nonprogressive course after initial gait deterioration. Autosomal recessive ataxia with ocular apraxia is a progressive condition allowing, in any case, very long survivals until late adulthood.

One hundred seven patients in 80 families with recessive ataxia have been identified so far through our survey in Portugal. Friedreich ataxia, as expected, is the most frequent diagnosis (38% of the patients), followed immediately by AOA (21% of the patients).

Based on our own experience and the findings of previous reports, we propose the following clinical criteria for AOA: (1) autosomal recessive transmission; (2) early

onset (for most patients in early childhood); (3) combination of cerebellar ataxia, ocular apraxia, and early areflexia, with the later appearance of a full picture of peripheral neuropathy; (4) absence of mental retardation, telangiectasia, and immunodeficiency; and (5) the possibility of a long survival, although with severe motor handicap.

Accepted for publication May 24, 2000.

This study was supported by grant 207 from the Comissão de Fomento da Investigação em Cuidados de Saúde (Portuguese Ministry of Health), Lisbon, and grants from Fundação para a Ciência e Tecnologia (Portuguese Ministry of Science and Technology) and the Portuguese Health Administration (projects STRDA/C/SAU/277/92 and PECS/C/SAU/219/95), Lisbon.

We thank all patients and their families for participating in this study, and their physicians for referring them to our national survey of hereditary ataxias and spastic paraplegias in Portugal.

Corresponding author and reprints: Paula Coutinho, MD, PhD, Division of Neurology, Department of Medicine, Hospital de São Sebastião, 4520-211 Santa Maria da Feira, Portugal (e-mail: pcoutinho@hospitalfeira.min-saude.pt).

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