LATE ONSET AUTOSOMAL DOMINANT CEREBELLAR ATAXIA

A FAMILY DESCRIPTION AND LINKAGE ANALYSIS WITH THE HLA SYSTEM

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SUMMARY — A family suffering an autosomal dominant form of late onset hereditary cerebellar ataxia is described. Eight affected family members were personally studied, and data from another four were obtained through anamnesis. The mean age of onset was 37.1±5.4 years (27-47 years). The clinical picture consisted basically of a pure ataxic cerebellar syndrome. CT-scan disclosed diffuse cerebellar atrophy with relative sparing of the brainstem (and no involvement of supratentorial structures. Neurophysiological studies (nerve conduction, VEP and BAEP) were normal. Twenty-six individuals were typed for HLA histocompatibility antigens. Lod scores were calculated with the computer program LINKMAP. Close linkage of the ataxia gene with the HLA system in this family could be excluded — 0==0,02, z=(—2,17) — and the overall analysis of the lod scores suggest another chromossomal location than chromosome 6.

Ataxia cerebelar hereditária de início tardio: descrição de uma família com estudo de ligação com o sistema HLA.

RESUMO — Descreve-se uma família afetada por forma autossômica dominante de ataria cerebelar de início tardio (acima dos 20 anos). Oito membros da família são estudados e dados de outros quatro afetados pela doença foram obtidos por anamnese. A média de idade de início da doença foi 37,1±5,4 anos (27-47 anos). O quadro clínico consistia basicamente de síndrome cerebelar de caráter lentamente progressivo, sem ocorrência concomitante de sinais ou sintomas decorrentes de envolvimento de outros sistemas. Estudo tomográfico computadorizado mostrava atrofia cerebelar difusa com relativa preservação do tronco cerebral e das estruturas supratentoriais. Estudos neurofisiolôgicos (neurocondução motora/sensitiva, potenciais evocados visuais e auditivos) foram normais. Vinte e seis pessoas da família foram tipados para antígenos de histocompatibilidade HLA. Escores lod foram calculados utilizando programa de computador denominado LINKMAP. Ligação estreita com o sistema HLA nesta família foi excluída — 0==0,02, z=(—2,17) — e a análise global dos escores lod sugerem que *o* gene mutante nesta família não se localiza no cromossomo 6.

Pierre Marie 22 reviewed the cases of cerebellar ataxia reported by Fraser, Nonne, Sanger-Brown and Klippel-Durant, and proposed the term «hérédoataxie cérébelleuse» to this hereditary form of ataxia distinct from that described by Friedreich. Since then additional reports on cases of hereditary cerebellar ataxia have been accumulated and several classifications of these disorders have been proposed 4,9,13,19. In most families described with late onset autosomal dominant cerebellar ataxia (mean onset age above 20 years), the affected members showed a complex clinical picture, most commonly including dementia, ophthalmoplegia, optic atrophy, extrapyramidal

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syndrome, amyotrophy, peripheral neuropathy, myoclonus and deafness 14. A gene linked to the HLA system on the short arm of chromosome 6 has been detected in some families 10,17,39. Nevertheless, genetic heterogeneity of this group of autosomal dominant cerebellar ataxia is likely 1.

A family with several members suffering a noncomplicated form of late onset autosomal dominant cerebellar ataxia is described and the results of linkage study with the HLA system are reported[2].

CASUIST1CS, METHODS AND RESULTS

This is the description of a family presenting an autosomal dominant form of cerebellar ataxia (Fig. 1). The proband patient (111-18) took her first consultation with us in November 1986. She and her sister's initial diagnosis was multiple sclerosis. The patient 1-1 was born in France and details of her disease were not obtainable. All the sibship (III) were born in the state Santa Catarina, Southern Brazil. The members 111-10, 111-18, 111-20, IV-2, IV-10, IV-26, IV-28 and IV-30 were admitted to our Service, where they were submitted to clinical laboratory tests, electrophysiological studies and CT-scan. The member 111-12 was affected and died in 1978. Data of his disease were obtained from his wife. The mean onset age was 37.1±5.4 years, with a range from 27 to 47. The age of onset did not differ significantly between the male (36.3±3.4) and female patients (39.2±8.6). The clinioal picture was quite uniform and consisted basically of a slowly progressive, cerebellar syndrome, with dysarthria, gait ataxia, and dysmetria of the upper limbs as the first clinical features. None of the family members suffered from the following signs/symptoms: dementia, ophthalmoplegia, optic atrophy, deafness, bulbar cranial palsies, postural hypotensoin, cogwheel rigidity, involuntary movements, fasciculations, amyotrophy, sensory disturbances, sphincteric dysfunction, and skeletal defprmities. Clinical, tomographic and electrophysiological findings are summarized in Table 1. Only individual IV-30 suffered epilepsy (primary generalized) since aged 7. An EEG was normal. She was medicated with carbamazepine and clonazepam with good control of her epileptic fits. No other member of this family suffered epilepsy. The affected individuals II-4, II-5, III-6 and 111-12 died at 80, 65, 67, and 62 years-old, respectively. The cause of death could not be elucidated. All family members of generation V were normal. Their ages ranged from 1.7 year to 26 years. A five-point clinical disability sciale28 was applied to 11 affected family members. The progression rate (degree of disability/years from onset) was calculated for each affected member and plotted against the age of onset with the use of the Spearman's correlation coefficient. No significant correlation was observed between these two parameters. On the other hand, a significant positive correlation rate was found between the duration of disease and the grade of disability (rs t= 0.826, p < 0.01).

Laboratory tests — The following laboratory tests were performed for 8 of the affected individuals, with normal or negative results: complete hemogram, erythrocyte sedimentation rate, VDRL, sodium, potassium, calcium, phosphorus, cholesterol, triglycerides. BUN, creatinine, glucose, uric acid, T3, T4 and TSH, hepatic transaminases. Cerebrospinal fluid examination, including protein electrophoresis, was performed in 7 affected family members and was normal in all of them. Electrocardiogram and chest X-ray were performed in 8 affected individuals and were normal.

HLA-typing and linkage study — Blood samples were obtained from 8 affected family members, 12 free of the disease, and 6 at risk. Lymphocytes were isolated from heparinized blood by a ficoll-hypaque method 6 and were typed for histocompatibility antigens by a microlymphocytotoxicity techniques. The panel of antisera included reagents from the 8th and 9th International Histocompatibility Workshops and local antisera for typing of 17 HLA-A, 32 HLA-B, and 8 HLA-C specificities. Lod scores were calculated with the computer program LINKMAP21. The results are depicted in Table 2.

Electrophysiological studies — Nerve conduction studies (motor and sensory) were performed in patients 111-20, IV-2, IV-10, and IV-30 by conventional methods, and the results were within normal range. Pattern-reversal visual evoked potential and brainstem evoked potential studies were performed in 7 affected individuals (111-18, 111-20, IV-2, IV-26, IV-28, and IV-30), and were normal.

CT-scan examinations — Eight affected family members were examined with a Tomoscan 305 (matrix 254x254, Phillips, Netherlands). The scanning plane was parallel to the orbito-meatal line. Slice thickness was 3mm for the posterior fossa evaluation. In all patients,

	Generation III			Generation IV				
	10	18	20	2	10	26	28	27
Age of onset	38	47	43	40	35	37	31	27
Present age	65	61	60	45	41	41	36	39
Dysarthria	+	+	+	+	+	+	+	+
Dysmetria								
Upper limbs	+	+	+	+	+	+	+	+
Lower limbs	+	+	+	0	+	0	+	+
Dysdiadochokinesia	+	+	+	+	+	0	+	+
Nystagmus	+	+	+	+	+	0	+	+
Normoreflexia	+	+	+	+	+	+	+	+
Ataxic gait	+	0	0	+	+	0	+	+
Bedridden	0	+	+	0	0	0	0	0
Holmes manouvre	+	+	+	0	+	0	0	+
Hypotonia	+	+	+	0	+	0	0	+
Cerebellar tremor	+	+	+	+	+	0	+	+
CT-scan								
Cerebellar atrophy	+ + +	+ + +	+ + +	+ +	+ + +	+	+	+ +
Brainstem atrophy	+ +	+	0	0	0	0	0	+
Neuroconduction	—	—	N	N	N	—	—	N
VEP study	—	N	N	N	N	N	N	N
BAEP study	—	N	N	N	N	N	N	N

Table 1 — Summary of clinical, radiological and electrophysiological findings in individuals with ataxia.
Clinical findings: + present, 0 absent. CT-scan findings: + + + severe, + + moderate, + mild, 0 absent. Motor and sensory neuroconduction, VEP and BAEP studies: (—) not done; N, normal.

Recombination fraction (o)	Lod scores (z)
0.01	—2.78
0.02	—2.17
0.05	—1.38
0.10	—0.80
0.15	—0.49
0.20	—0.29
0.25	—0.16
0.30	—0.08
0.35	—0.04
0.40	—0.01
0.45	—0.00

Table 2 — Lod scores (z) for the cerebellar ataxia locus in relation to HLA.

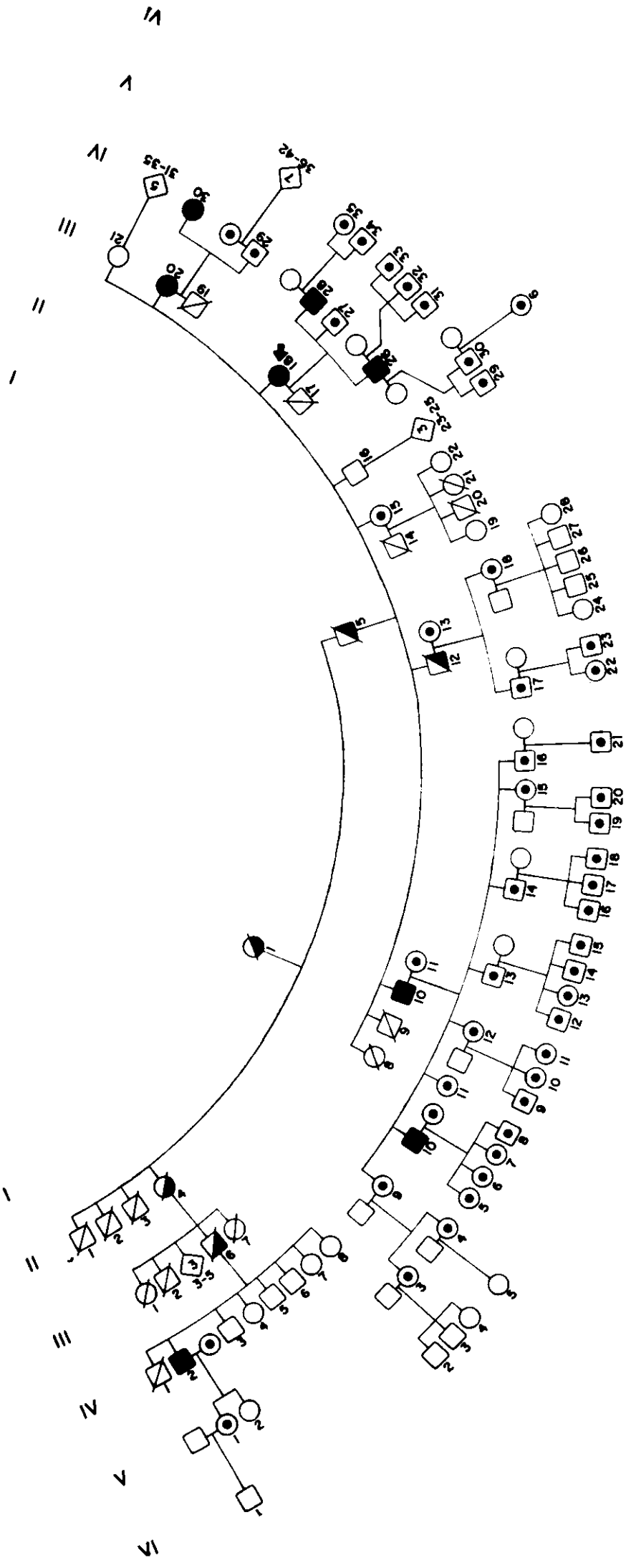

Fig. 1 — Pedigree of the family with autosomal dominant cerebellar ataxia. Arrow indicates the proband. Dotted figures are the individuals interviewed and examined by the authors (WOA, MAC).

ADCA TYPE I	— with optic atrophy/ophthalmoplegia/dementia extrapyramidal features/ amyotrophy
ADCA TYPE II	— with pigmentary retinal degeneration ± ophthalmoplegia and/or extrapyramidal features
ADCA TYPE III	— «pure» autosomal dominant cerebellar ataxia of later onset
ADCA TYPE IV	— with myoclonus and deafness

Table 3 — Classification of autosomal dominant cerebellar ataxia (ADCA) (Harding, 1982).

with the exception of patient IV-26, there was widening and increase of number of the hemispheral and vermian cerebellar sulci. In earlier cases (e.g., case IV-26), the atrophy was almost limited to the anterior portion of the vermis. The dimensions of the brainstem .and fourth ventricle were normal, as well as the supratentorial structures.

Therapeutic trials — Patients IV-10, IV-26 and IV-28 were medicated with choline chloride l.Og tid, baclofen lOmg tid, sodium valproat 500mg tid, each one tor three months, with one month of washout period between each drug. No subjective nor objective improvement could be observed. Patient IV-28 received intramuscular i.00 ug of *T^LH* (thyrotropin releasing hormone) each day, for 30 days, without improvement.

COMMENTS

The family described has a late onset form (mean age of onset after 20 years) of hereditary ataxia[14]. The mode of inheritance is clearly autosomal dominant. The involvement of other neurological systems leading to a complex clinical picture besides the cerebellar syndrome is the rule rather the exception in this proup of neurogenetic diseases. Therefore, Oppenheimer proposed the denomination of «multiple system atrophy»[26].

«Pure» hereditary cerebellar ataxia as observed in this family is uncommon[17-23]. Stone[32], in 1933, made the first description of a family affected by this form of hereditary ataxia, but only Harding[12], in 1982, proposed a distinct position for this kind of ataxia (Table 3). The age of onset observed by other authors is usually around the middle age, sometimes only over 60 years 12,30, differing significantly from the family hereby described. The Hoffmann's cases 15, where the debut of the disease was before the age of 40 in some affected members, an acute febrile illness seems to have triggered the disease, a fact not observed by other authors and by ourselves. We believe this observation is in keeping with the genetic heterogeneity within this group of «pure» form of heredoataxia, and emphasizes the provisional character of the clinical classification proposed by Harding 13. Electrophysiological (neuroconduction studies, BAEP, VEP and SSEP) and neuroimaging methods (CT-scan, MRI) seems to give little help to a better identification of distinct forms of hereditary ataxias, for their findings are not specific, and they give few data regarding the pathogenesis of these diseases^. Electro-oculographic studies may help in detecting potential new cases in some families, giving support to a better genetic counseling, but there are few works in this field 8,16.

The final step to classify the autosomal dominant hereditary ataxias will be the mapping and identification of the mutant genes. Several authors studied the possibility of the presence of the ataxia gene locus on the sixth chromosome near the HLA loci 3,10,18,20,23,25,27,34,37,38. i$_n$ only three families, linkage with HLA could be shown 10,17,39. The reported recombination fraction was around 20%. Although the mutant genes of these families are syntenic (located in the same chromosome), they seem to differ, since in two families they are centromeric 38,40, and in the third one, telomeric with respect to HLA[29]. Besides this, the two families, in which the ataxia locus was mapped centromeric to HLA, have a quite different phenotypic expression of the disease[7.39]. This observation suggests the occurrence of different mutations in the same locus. In some studies, linkage with the HLA system could excluded for recombination fractions less than 10-20%, suggesting the existence of at least one ataxia gene different from the one assigned to chromosome 6. In fact, the gene locus of Machado-Joseph's disease, another form of autosomal dominant ataxia (ADCA Typel), has been mapped on the first chromosome[31].

In the family hereby described, close linkage of the ataxia gene with the HLA system could be excluded (Table 2), and the overall analysis of the lod scores obtained suggests another chromosomal location.

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