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On an autosomal dominant form of retinal-cerebellar degeneration: an autopsy study of five patients in one family

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Abstract We describe a family with an autosomal dominant form of retinal-cerebellar atrophy. There is an extreme variability in age of onset and severity of the clinical symptoms: some patients remain nearly asymptomatic throughout their entire life; others develop severe retinal and cerebellar symptoms after the age of 35 years; others suffer from a severe disorder with onset in adolescence and death during the third decade of life; in others the onset is in early childhood with prevalence of cerebellar symptoms. There is neither dementia nor epilepsy in any of the patients. Four out of five autopsies showed a severe retinal atrophy, and all five autopsies were also characterized by (1) a cerebellar atrophy affecting the spinocerebellar and olivocerebellar tracts, the cerebellar cortex and the efferent cerebellar pathways, (2) an involvement of the pyramidal pathways and of the motor neurons of brain stem and spinal cord, and (3) an atrophy of the subthalamic nucleus and to a much lesser extent of the pallidum, with also some damage to the substantia nigra. The posterior columns are much less affected except in one patient. In this family, we have excluded linkage with the two loci for spinocerebellar ataxia, i.e., SCA1 on chromosome 6p and SCA2 on chromosome 12q as well as with the locus for Machado-Joseph disease (MJD) on chromosome 14q. A genome-wide search is currently being performed to detect the disease locus responsible.

Key words Autosomal dominant disease
Cone dystrophy · Cerebellar atrophy
Multiple system atrophy · Linkage

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Introduction

Hereditary cerebellar ataxias represent a heterogeneous group of disorders characterized by a progressive cerebellar syndrome associated with a wide scale of additional anomalies [15].

The exact classification of the different inherited cerebellar ataxias will remain a semantic discussion between splitters and lumpers until the localization or identification of the different genes responsible for these different entities has been realized. Linkage analysis has assigned the gene responsible for ataxia telangiectasia to chromosome 11 [9] and the gene responsible for Friedreich's ataxia to chromosome 9 [4]. In addition, a gene encoding a dominant spinocerebellar atrophy (SCA1) was initially linked to the HLA complex on the short arm of chromosome 6 [20, 24, 33] before being

more accurately localized on 6p22-p23 and shown to be associated with a trinucleotide repeat expansion [23]. However, linkage with the SCA1 gene has not been found in every family with autosomal dominant cerebellar ataxia [1]. Another disease locus, designated SCA2, has been shown to be responsible in other large families [17] and linkage of SCA2 with chromosome 12q23–24.1 has been recently demonstrated [10]. Another autosomal dominant multisystem disorder, Machado-Joseph disease (MJD), originally described in Portuguese patients and characterized by cerebellar ataxia, nystagmus, dysarthria, pyramidal signs, external ophthalmoplegia, dystonia, athetotic movements and muscular atrophy, has been shown to map to chromosome 14q [28].

We report five autopsies in a family with autosomal dominant retinal-cerebellar degeneration with extremely variable age of onset and symptoms, and not linked to the SCA1, SCA2 or MJD loci.

Material and methods

Clinical data

We performed a genealogical study of the whole family, and neurological examination, laboratory work-up, neurophysiology and neuroradiology on the patients.

Neuropathological methods

After formalin fixation during 6 weeks, paraffin sections were stained for cytology (cresyl violet, haematoxylin eosin, Masson's trichrome), myelin (Klüver-Barrera's method) and axons (Bodian's method); frozen sections for myelin (Spielmeyer's method), cytology (cresyl violet), fibrillary glia (Holzer's method), neutral fats (Sudan III) and lipopigments, vic glycol radicals, etc. (PAS method). We searched for senile plaques and neurofibrillary tangles with Von Braunmühl's method. Finally celloidin sections were stained for cytology (Nissl's method) and myelin (Woelcke-Heidenhain's method).

Paraffin slides of the optic nerves were stained by polyclonal antibodies (pAb) against glial fibrillary acidic protein (GFAP) and myelin basic protein (MBP) (dilutions of 1/2.000 and 1/1.000, respectively; peroxidase-antiperoxidase method) and by a monoclonal antibody (mAb) 6B9 against neurofilaments (dilution of 1/20.000; avidin-biotin-complex method) [26]. The pAb against GFAP is a rabbit anti-cow GFAP (Dako, Glostrup, Denmark). The pAb against MBP is a rabbit anti-MBP (Neurochemistry laboratory, Born-Bunge Foundation). The mAb 6B9 is a mouse anti-neurofilament antibody (Innogenetics, Ghent). The incubation was overnight at room temperature.

Electron microscopy was performed on autopsy material from three patients (patients 1, 2 and 5) according to standard methods including fixation in buffered glutaraldehyde, post-fixation in osmium tetroxide, araldite embedding and contrasting with uranyl acetate and lead citrate followed by examination with a Philips CM10 electron microscope. The areas examined were the frontal cortex, the optic nerve, the cerebellar cortex, a spinal ganglion, the fibular nerve and the fibularis longus muscle.

DNA studies

Blood samples were collected by venipuncture of affected, unaffected and at-risk individuals and DNA was extracted. The members of the family whose blood had been used for linkage analysis (40 persons including 10 patients) are indicated by an asterisk in the family tree (Fig. 1).

The primer sequences used in the amplification with the polymerase chain reaction (PCR) technique of the dinucleotide repeat polymorphisms at the loci D6S89, D6S109, D12S79, D12S105 and D14S48 were as published [10, 28, 33]. The PCR reactions and detection of polymorphic alleles was performed as reported elsewhere [29]. Pairwise linkage analysis for the DNA marker loci was performed using the allele frequencies calculated in the family with the program PRIMITIV provided by L. Sandkuyl. Linkage was calculated using the program MLINK from the computer package LINKAGE version 5.1, with the appropriate corrections for age-dependent disease penetrance based on the mean onset age of the disease per generation.

Results

Clinical data (Table 1)

Preliminary data on four patients have been reported previously by some of us [21, 25]. An abridged pedigree of the family is shown in Fig. 1; most of the family members live in the south of Belgium and a few in France; they exert mainly administrative or managing functions and are not exposed to toxic hazards.

The classical course of this dominantly inherited familial disorder was as follows: onset between the age of 10 to 25 years with (1) visual disturbances affecting the perception of colors, and (2) gait ataxia with a less severe kinetic ataxia. Pyramidal signs developed progressively with hyperactive deep tendon reflexes, absent abdominal cutaneous reflexes, ankle clonus and Babinski's signs. Vestibular areflexia, dysarthria and dysphagia appeared frequently. Bronchopneumonia was the most frequent cause of death. We observed neither dementia, epilepsy nor undue risk of developing carcinoma. None of the patients took any form of medication which could be considered neurotoxic. None had noticeable immunological abnormalities.

A wide clinical intrafamilial variability in age of onset and symptoms existed. Three variants were recognized: (1) in children (e.g., VI 85 or VII 9) the disorder presented with a very early onset between the age of 18 months and 3 years with cerebellar ataxia; (2) some patients (e.g., IV 12 or IV 17) had a late onset of the disease between the ages of 35 and 65 years with prevalent visual and cerebellar features; and (3) some adult family members shown to be at risk or asymptomatic gene carriers by genealogical work-up had either minimal signs such as mild dysarthria or barely discernable gait unsteadiness or seemed to be clinically unaffected. When we performed technical investigations on such people (V 13, V 18, V 23), we diagnosed retinal involvement by fundoscopy, angiofluorography, or electroretinography (ERG) and cerebellar atrophy by magnetic resonance imaging (MRI) . Visual problems are developing in at least two other adult individuals (V 31 born in 1949 and V 46 born in 1958).

Various ophthalmoscopic features have been reported such as stippling of the macular area, macular

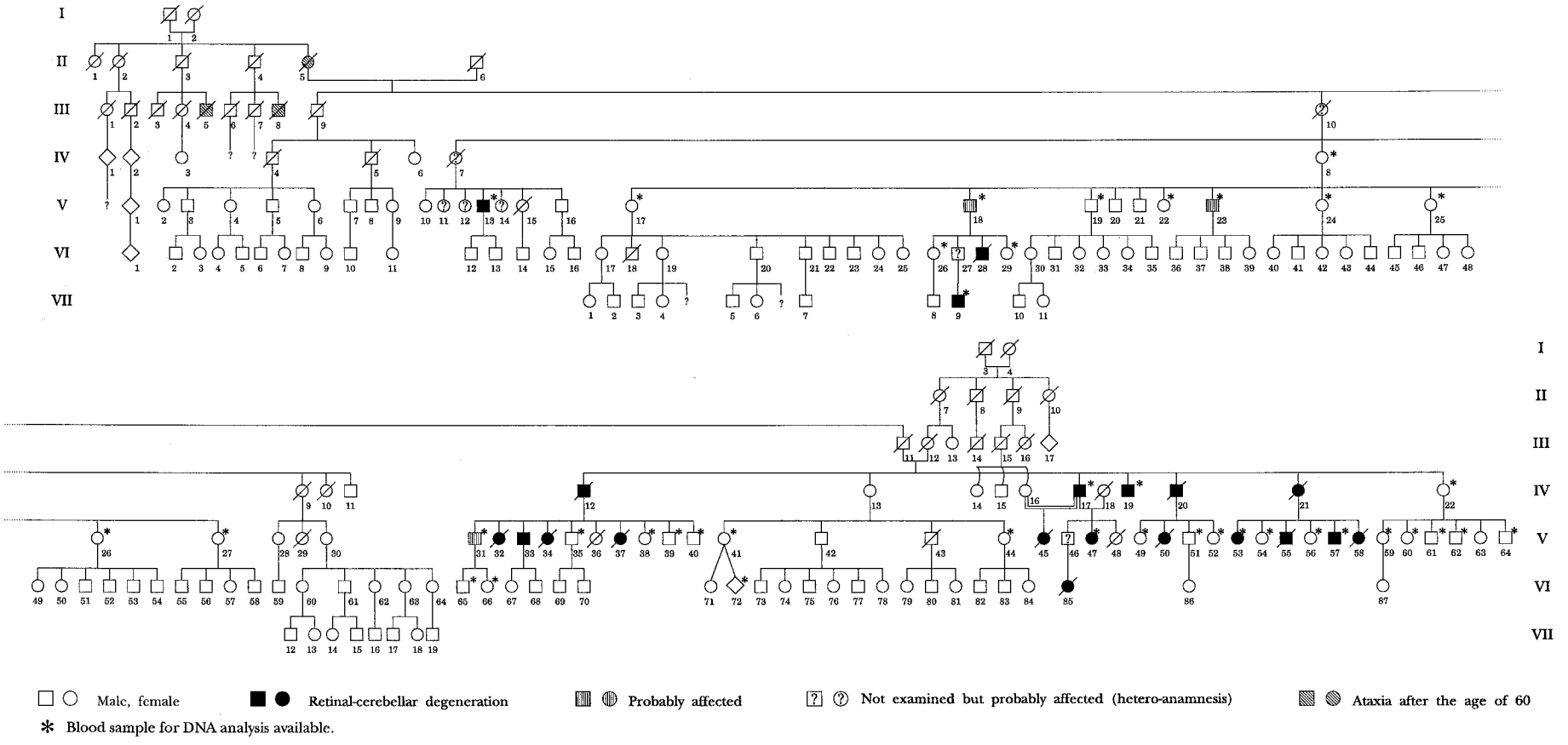

Fig. 1 Family pedigree

Table 1 Summary of the main clinical features

Patient	Sex	Onset	Clinical features	Laboratory work-up	Death
IV 21	F	15	Progressive ataxia. Could no longer walk alone at age 34. Decrease of visual acuity from the age of 20 years on; blindness and optic atrophy at age 41. At age 47, blindness, truncal ataxia, dysmetria, dysarthria, impaired proprioception, pyramidal signs.	Vestibular areflexia. Delayed somatosensory evoked potentials (SSEP) after stimulation of the upper limbs, absent after stimulation of the lower limbs.	54
V 55 Son of patient 1	M	12	Loss of balance, decrease of eyesight and macular changes. At age 20, ataxo-spastic gait, dysarthria, mild pyramidal signs and impairment of the proprioception. Dysmetria in all four limbs. Ocular movements were limited. Patient stayed at home until death.	Vestibular areflexia. Normal (Nl) SSEP of the upper limbs. Increased latencies after stimulation of the lower limbs.	28
V 58 Daughter of patient 1	F	10	Decrease of visual acuity and ataxic gait as first signs. At age 14, ataxic gait, mild pyramidal signs. Hypermetria in the upper limbs. At age 22, blindness and cerebellar ataxia. No neuroradiology. Bronchopneumonia as the other patients.	Vestibular areflexia. Nl SSEP from the upper limbs, not elicited by stimulation of the lower limbs. Nl motor conduction velocities of both fibular nerves (47 m/s).	26
VI 28	M	13	Decrease of visual acuity at age 13, further decrease to 2/10 at age 16. Cerebellar ataxia, clumsiness and dysarthria, retinal pigmentary degeneration [25] and Babinski's signs. At age 20, cerebellar syndrome, very slow ocular saccades, no optokinetic nystagmus. At age 24, non-demented patient with severe cerebellar ataxia, blindness, ophthalmoplegia, dysarthria, paralysis of the pharyngeal wall and bipyramidal syndrome. Normal proprioception. Athetoid movements and segmental myoclonus.	Nl CSF, motor and sensory conduction velocities. Nl conjunctival biopsy. No visual evoked potentials. Brainstem auditory evoked potentials compatible with a retrocochlear involvement. SSEP showed damage to the posterior columns and lemniscal pathways. Nl plasmatic and urinary assays of amino-acids, organic acids, pipecolic acid, phytanic acid and very long chain fatty acids. Severe cerebellar atrophyon MRI	26
VI 85	F	3	Progressive cerebellar ataxia and dysmetria. No initial pyramidal features. Normal ocular movements. At the age of 4, severe intentional tremor and ataxia causing frequent falls. Cerebellar type of dysarthria. Dysphagia, increased tremor of the head, hyperactive deep tendon reflexes and equivocal cutaneous plantar responses 5 months later. Normal eye fundi but decreased visual acuity to half the normal value. At the age of 5, palpebral ptosis, poor ocular fixation, intentional tremor of head, neck, trunk and extremities. No Babinski's signs. Apnoea and cardiac arrest caused death two months later.	Nl peripheral motor conduction velocities. MRI revealed a very severe cerebellar atrophy. Photopic electroretinogram of low amplitude. Delayed responses to flash evoked visual potentials .	5

hole or bull's eye [21, 30]. The transmission of the disorder is autosomal dominant with apparently complete penetrance. The wide clinical spectrum in this family follows a clear pattern of anticipation, the younger patients having earlier initial symptoms, a more severe course and earlier death. In such examples, the transmission of the disease is by the father. Table 1 contains specific clinical information concerning the autopsied patients.

Neuropathological data (Table 2)

Table 2 summarizes the main features which are further illustrated in Figs. 2–5.

DNA studies

Linkage analysis was performed with polymorphic dinucleotide repeat markers flanking the SCA1 and

Table 2 Summary of the main neuropathological features (*LM* light microscopy, *EM* electron microscopy)

Patient	Age at death	Neuropathology
IV 21	54	**Gross examination** Low normal brain weight (1,154 g.). Atrophy of cerebellum, optic nerves, optic chiasm. In the retina, atrophic and "osteoblastic" areas showing a confluence of pigment. **LM** (1) In the retina, atrophy of the choroid, degeneration of the cells of the retinal pigment epithelium, penetration of pigmented cells in the retinal layers, total loss of the photoreceptors, bipolar cells and ganglion cells. (2) Atrophy, myelin pallor and fibrillary gliosis of optic nerves, optic chiasm and optic tracts; atrophy of lateral geniculate nucleus with neuronal losses; myelin pallor of optic radiations. (3) Myelin pallor and gliosis of the dorsal and ventral spinocerebellar tracts, olivocerebellar tracts and dentato-rubro-thalamic pathways. (4) Atrophy of the subthalamic nucleus and slight pallidal atrophy. (5) Neuronal losses in the bulbar motor nuclei and in the anterior horns of the spinal cord. (6) Myelin pallor in posterior columns and pyramidal pathways. **EM** Loss of granule cells in the cerebellar cortex. No paired helical filaments, senile plaques or signs of intraneuronal storage. Normal fibular nerve. Neurogenic atrophy of the peroneal muscle. Loss of photoreceptors replaced by hypertrophic Müller cells, detachment of cells of the retinal pigment epithelium from Bruch's membrane migrating towards the retina through the external limiting membrane, infiltration of the atrophic retina by macrophages containing granules of melanin. Loss of myelinated fibers in the optic nerve, abundant fibrillary astrocytes.
V 55	28	**Gross examination** Normal brain weight (1,282 g.). Atrophy of cerebellum and optic pathways. **LM** (1) In the retina, atrophy and of hypertrophy of the pigmentary epithelial cell layer, total loss of photoreceptors , atrophy of the bipolar cell layer coming into direct contact with the cells of the retinal pigment epithelium. Macrophages containing melanin granules infiltrate the bipolar cell layer. Few ganglion cells left. (2) Myelin pallor, axonal losses and fibrillary gliosis of optic nerves, optic chiasm and optic tracts; rarefactions of neurons in the lateral geniculate body; myelin pallor of the optic radiations. (3) Myelin pallor of spinocerebellar tracts, olivocerebellar tracts and cerebellar cortex; dentato-thalamic atrophy with small brachia conjunctiva. (4) Atrophy of subthalamic nucleus and milder pallidal atrophy. (5) Mild neuronal losses in the nucleus of the common oculomotor nerve, more severe loss in the bulbar motor nuclei and in the anterior horns. (6) Very slight involvement of the pyramidal pathways in the spinal cord. **EM** Normal tibial and phrenic nerves; neurogenic atrophy in the peroneal muscles. No intralysosomal storage. Losses of myelinated axons and fibrillary gliosis in the optic nerves.
V 58	26	**Gross examination** Atrophy of optic pathways and cerebellum. **LM** (1) Retinal lesions identical to the ones found in the previous patients. (2) Atrophy and myelin pallor of optic nerves, optic chiasm, optic tracts; moderate neuronal losses in the lateral geniculate nucleus and slight myelin pallor of the optic radiations. Immunohistochemistry of the optic nerve showed a pallor with an antibody against myelin basic protein. Decrease of the number of axons using a monoclonal antibody against neurofilaments and increase of the glial fibrillary acidic positive cells as compared with controls. (3) Myelin pallor of spinocerebellar and olivocerebellar tracts; cerebellar cortical atrophy; dentato-thalamic atrophy. (4) Neuronal rarefactions in the corpus subthalamicum. (5) Neuronal losses in the motor nuclei of the medulla oblongata and in the anterior horns of the spinal cord. (6) Moderate involvement of the pyramidal pathways in the spinal cord.
VI 28	26	**Gross examination** Brain weight=1,120 g. Small lateral geniculate bodies and severe atrophy of the cerebellum. **LM** (1) Some focal migration of melanin into the outer nuclear layer, total loss of photoreceptors and decreased number of the bipolar and ganglion cells. (2) Atrophy and slight myelin pallor of the optic tract, moderate neuronal losses and astrocytic gliosis in the lateral geniculate body. (3) Myelin pallor of the spinocerebellar, spinothalamic, olivocerebellar tracts, almost complete loss of the Purkinje cells, marked atrophy of the dentate nucleus , myelin pallor and gliosis of the cerebellar white matter and brachium conjunctivum. Normal brachium pontis.

(continued on next page)

Table 2 (continued)

Patient	Age at death	Neuropathology
		(4) Prominent neuronal rarefactions and gliosis in the corpus subthalamicum and nucleus ruber, and to a lesser extent in the globus pallidus and substantia nigra (5) Severe neuronal losses in the bulbar olivary nuclei, neuronal rarefactions and fibrillary gliosis in the vestibular and hypoglossal nuclei, moderate neuronal rarefactions in the anterior horns and severe losses in Clarke's columns. (6) Slight myelin pallor of posterior columns and medial lemniscus. Normal pyramidal pathways.
VI 85	5	**Gross examination** Severe cerebellar atrophy. **LM** (1) Normal amounts of photoreceptors, normal bipolar cell layer and normal amounts of ganglion cells. The retinal pigment epithelium was normal. No lesions in the optic pathways. (2) Neuronal losses in the Clarke' s columns and loss of myelinated fibres of the direct and crossed spinocerebellar tracts. (3) Complete loss of Purkinje cells and marked reduction of the granule cells in the cerebellar cortex. (4) Atrophy of the dentate nucleus with myelin pallor of the superior cerebellar peduncles. (5) Decrease of the number of neurons in various motor nuclei of the brain stem (III and XII) and neuronal losses in the anterior horns of the spinal cord. (6) Loss of myelinated fibres of the gracilis and cuneate fascicles, neuronal losses in the gracilis and cuneate nuclei, myelin pallor in the lemniscal pathways, neuronal rarefactions in the thalamic nucleus ventralis posterior. No lesions in pallidum, corpus subthalamicum or pyramidal pathways. **EM** Loss of the Purkinje cells. No decrease of myelinated axons in the optic nerves, replacement of half the spinal ganglion cells by increased numbers of satellite cells and decrease of myelinated axons in the sciatic nerve. Small-field atrophy in the iliopsoas muscle.

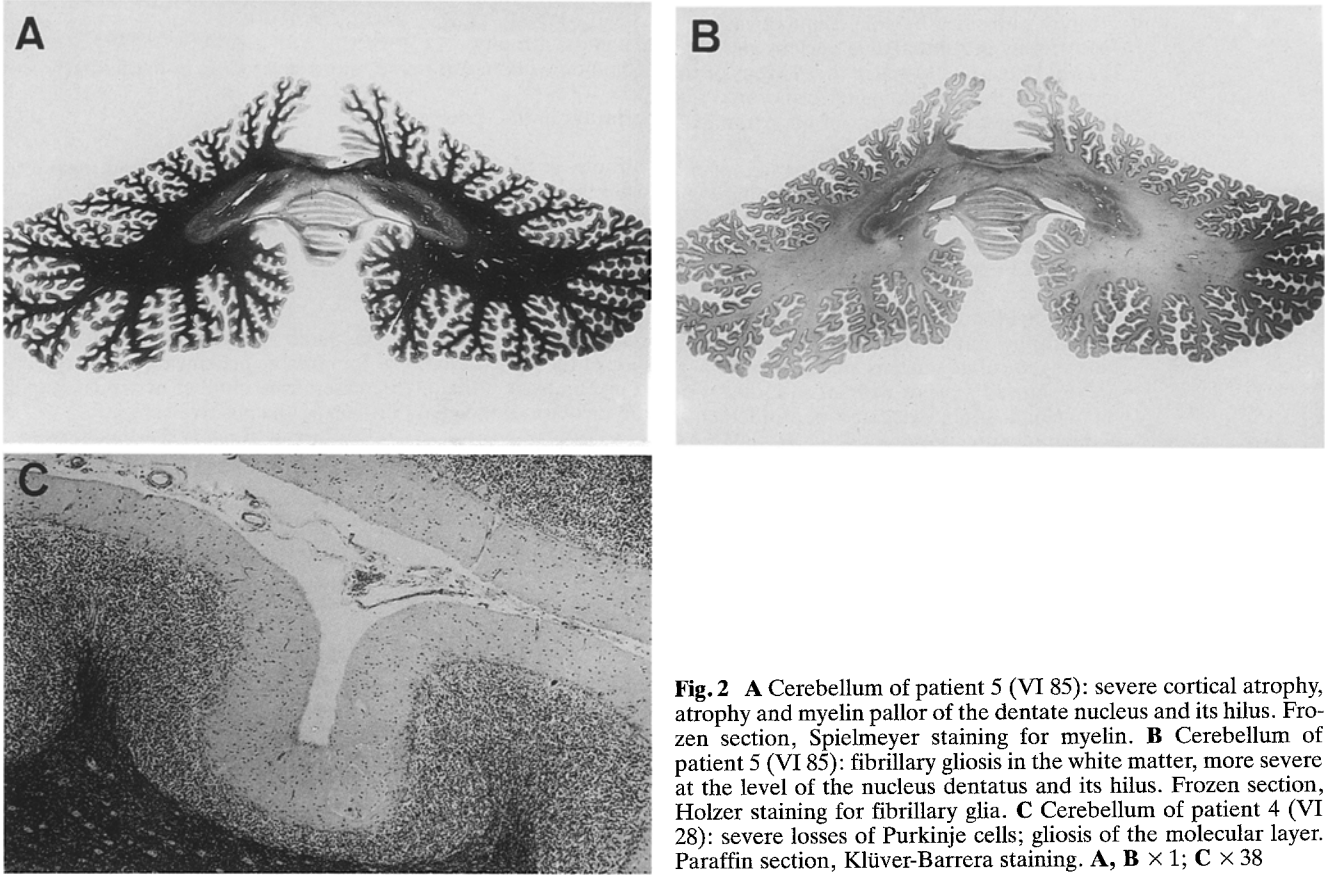

Fig. 2 **A** Cerebellum of patient 5 (VI 85): severe cortical atrophy, atrophy and myelin pallor of the dentate nucleus and its hilus. Frozen section, Spielmeyer staining for myelin. **B** Cerebellum of patient 5 (VI 85): fibrillary gliosis in the white matter, more severe at the level of the nucleus dentatus and its hilus. Frozen section, Holzer staining for fibrillary glia. **C** Cerebellum of patient 4 (VI 28): severe losses of Purkinje cells; gliosis of the molecular layer. Paraffin section, Klüver-Barrera staining. **A, B** × 1; **C** × 38

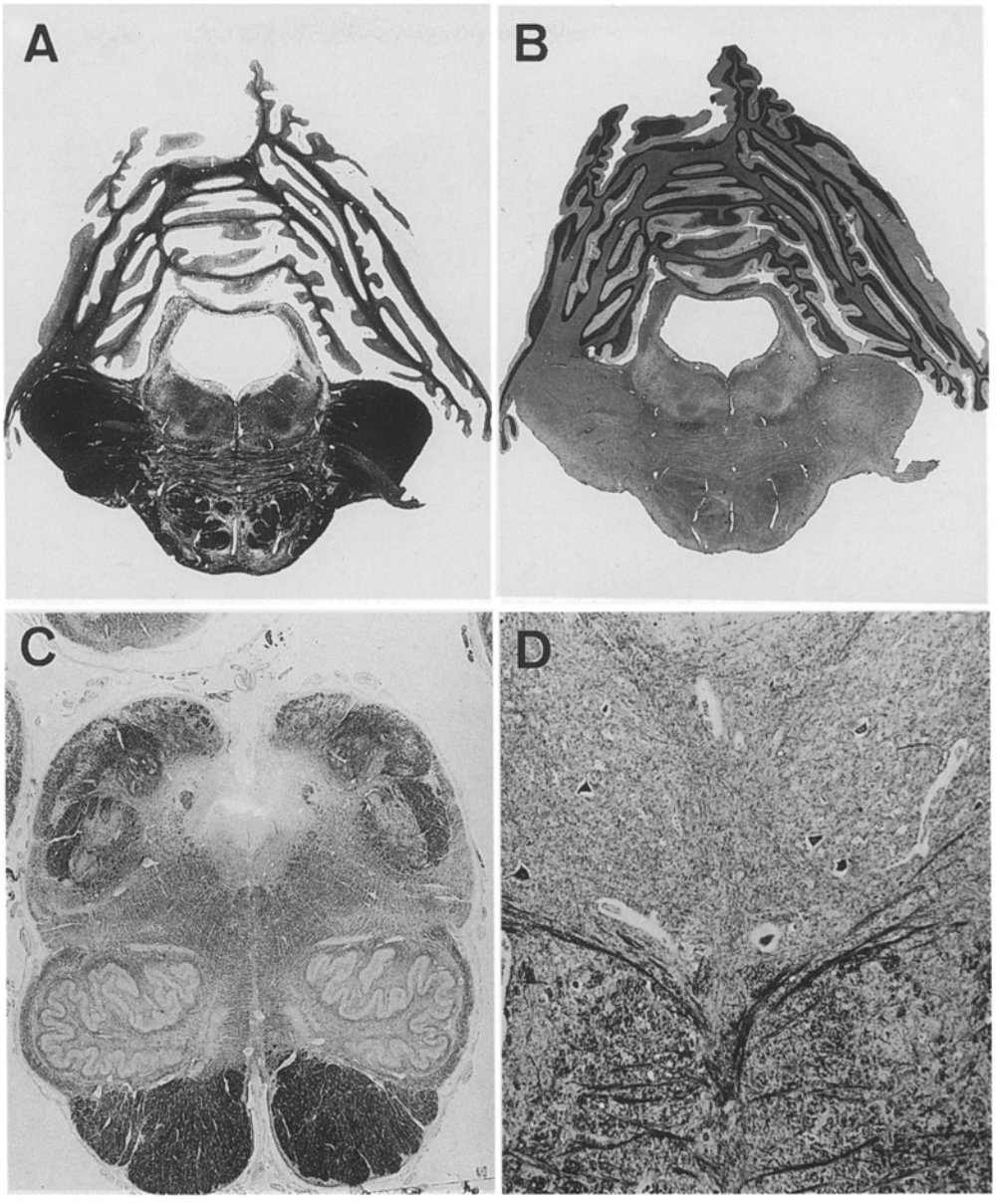

Fig. 3 **A** Pons of patient 1 (IV 21): the brachia pontis are intact, atrophy of the brachia conjunctiva. Frozen section, Spielmeyer staining for myelin. **B** Pons of patient 1 (IV 21): fibrillary gliosis of the atrophic brachia conjunctiva and of the medial and lateral lemniscal pathways, slight fibrillary gliosis of the pyramidal pathways. Frozen section, Holzer staining for fibrillary glia. **C** Medulla oblongata of patient 4 (VI 28): demyelination and atrophy of the nucleus olivaris principalis, pallor of the retrolatero-olivary areas, atrophy of the restiform bodies. Paraffin section, Klüver-Barrera staining. **D** Medulla oblongata of patient 4 (VI 28): neuronal losses in the nucleus hypoglossus. Paraffin section, Klüver-Barrera staining. **A, B** × 1.6; **C** × 5.7; **D** × 43

SCA2 loci on chromosomes 6 and 12, respectively. The SCA1 gene was localized on chromosome 6p22-p23 in the 7 cM interval flanked by D6S89 and D6S109, and shown to be associated with a trinucleotide repeat expansion [23]. We tested D6S89 and D6S109 and excluded (lod score <–2) linkage to both markers with exclusion distances of 16 and 3 cM, respectively. Also, we used PCR amplification to test whether the pathological CAG repeat expansion was present in the patients using the conditions described by Orr et al. [23]. Allele sizes of the CAG repeat were within the normal range, confirming the exclusion of the SCA1 locus based on linkage data. The SCA2 gene was recently localized on chromosome 12q24–24.1 between D12S58 end PLA2 [10]. We used D12S79 and D12S105 flanking the SCA2 gene over a distance of 5 cM (G. Auburger, personal communication). Again negative linkage data were obtained with exclusion distance of 11 cM and 18 cM for D12S105 and D12S79, respectively. We also analyzed linkage with D14S48 located in 14q24.3-q32 and showing a conclusive linkage to MJD in one family and suggestive linkage in other families [28]. Negative-linkage results were obtained and an exclusion distance of 3 cM was calculated. Our results significantly exclude the chromosomal regions spanning the SCA1 and SCA2 loci as the site for the disease gene in our family. Also, the results obtained with the chromosome 14q marker make it unlikely that the disease gene is located within the MJD region. However, since the MJD region spans a region of 29 cM between the markers D14S53 and D14S45, linkage analyses with additional markers are needed to exclude the whole MJD region [28].

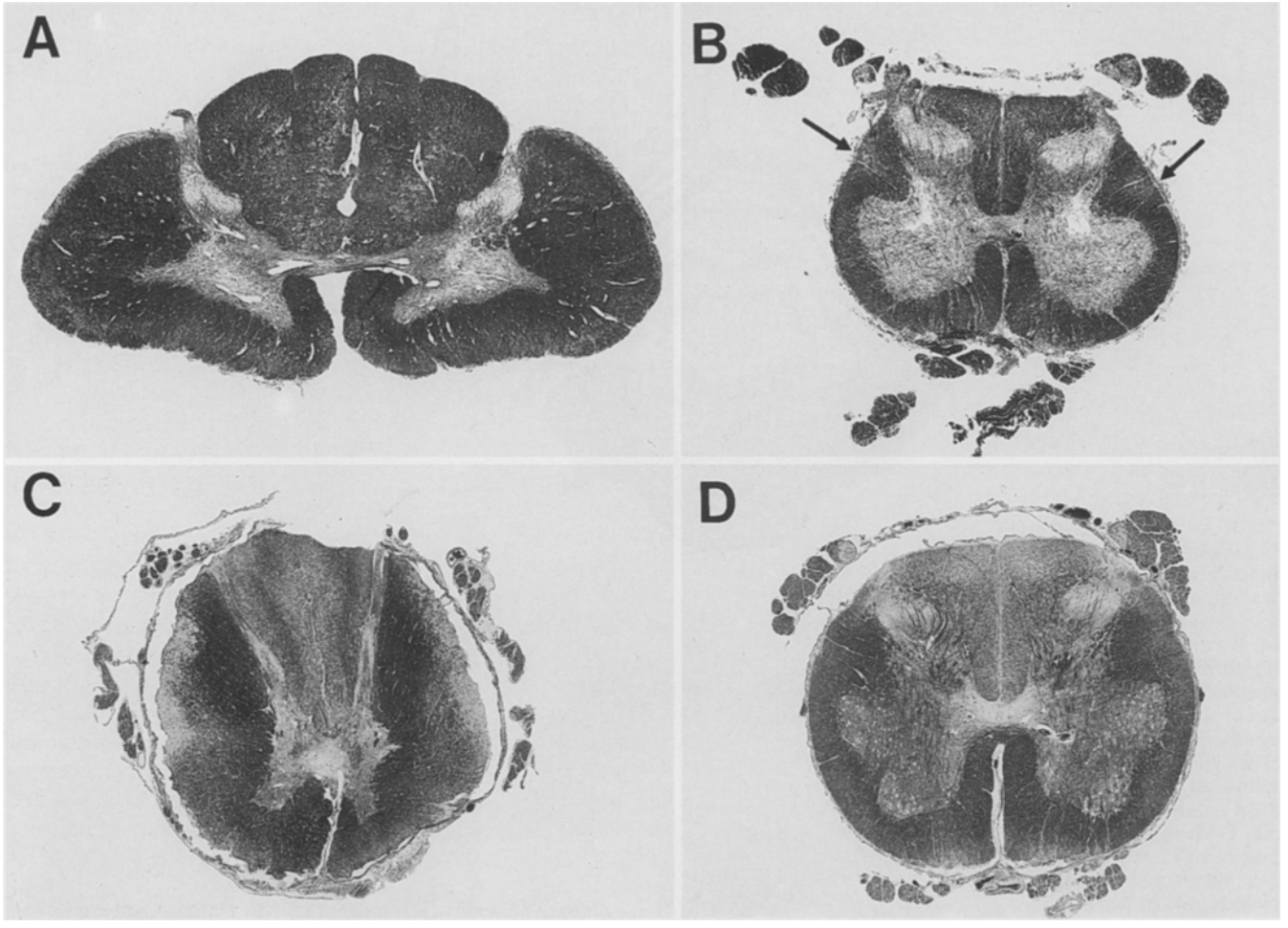

Fig. 4 **A** Cervical spinal cord of patient 1 (IV 21) at level C8: slight myelin pallor of the spinocerebellar tracts and of the posterior columns. Frozen section, Spielmeyer staining for myelin. **B** The same spinal cord at sacral level: slight myelin pallor of the crossed pyramidal pathways (*arrows*). Celloidin section, Woelcke-Heidenhain staining for myelin. **C** Thoracic spinal cord of patient 5 (VI 85): demyelination of the spinocerebellar tracts and of the posterior columns. Celloidin section, Woelcke-Heidenhain staining for myelin. **D** The same spinal cord at lumbo-sacral level: demyelination of the posterior columns. Celloidin section, Woelcke-Heidenhain staining for myelin. **A–D** × 7.9

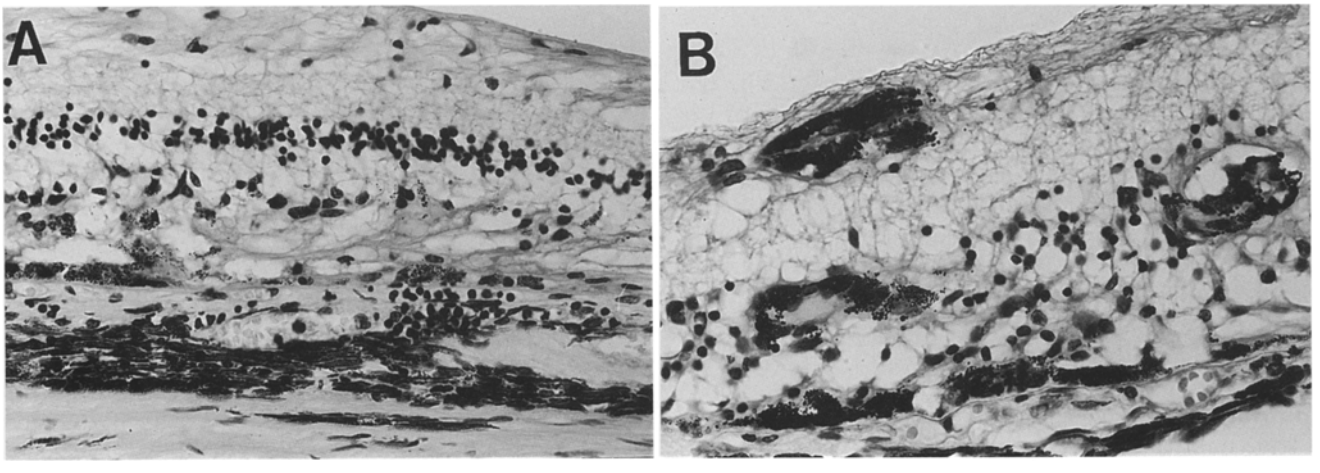

Fig. 5 **A** Retina of patient 1 (IV 21): loss of rods, cones and ganglion cells, penetration of cells with melanin pigment in the retinal layers. Paraffin section, haematoxylin-eosin staining. **B** Retina of patient 2 (V 55): total disarray of the retinal layers, loss of all photoreceptors and ganglionic cells, invasion of all retinal layers by melanin-laden macrophages. Paraffin section, haematoxylin-eosin staining. **A** × 258; **B** × 325

Discussion

This retino-cerebellar disorder has an autosomal dominant inheritance as patients have been identified in five successive generations, the male/female patient ratio is close to one and father to son transmission is documented. Considerable intrafamilial variability exists in age of onset, rate of progression, severity and occurrence of associated symptoms. The comparison of age of onset of the disease and also of the age of death, through generations II to VII shows very clearly the existence of a phenomenon of anticipation in the younger generations.

Neuropathological examination showed very similar lesions in all five patients. Some differences are probably due to differences in age of onset and death. For example, all the autopsied patients with the exception of the youngest patient (VI 85) showed a tapeto-retinal degeneration with total loss of cones and rods, loss of retinal ganglion cells and atrophy of the optic pathways especially in the pregeniculate segment. Spinocerebellar, olivocerebellar and dentato-rubro-thalamic pathways were approximately equally affected in all patients, whereas the cerebellar cortex and dentate nucleus showed neuronal losses. Atrophy of the corpus subthalamicum with less severe pallidal lesions was present in all cases except in the 5-year-old patient. Neuronal rarefactions were noted in the zona compacta of the substantia nigra of patients 1–4 but not in patient 5. Neuronal losses in the motor nuclei of the brain stem and the anterior horns existed in all patients, whereas the pallor of the pyramidal pathways in the spinal cord was most pronounced in patients 1 and 3. The posterior columns and the lemniscal pathways were only slightly involved in patients 1–4; only in case 5 was loss of myelinated fibres of the gracilis and cuneate fascicles present.

In summary, retina, optic pathways, spinocerebellar, olivocerebellar and efferent cerebellar tracts, cerebellar cortex were severely affected, while the proto- and the deuteromotor neurons and corpus subthalamicum were less severely involved. The fifth and by far the youngest patient had also more pronounced lesions in the posterior columns. The brachium pontis was not affected in any of the patients.

The disorder observed in our family could be differentiated from all heredo-ataxias and tapeto-retinal degenerations archived in the files of our Institute [18], families of late onset autosomal dominant cerebellar ataxias [14], hereditary spastic ataxias with retinal degeneration [2, 12], hereditary olivo-ponto-cerebellar atrophy (OPCA) with retinal degeneration [31], retinal degeneration and ataxia [3, 7], atrophic maculopathy with bull's eye lesions and OPCA [5], selective dysfunction of the cone system in autosomal dominant cerebellar ataxia [13], etc.

The histopathological lesions we observed are further to be distinguished from: (1) OPCA, since the ponto-cerebellar pathways were not involved; (2) Machado-Joseph disease [8, 32] because of different clinical features and ethnic origin and also because the cone-rod dystrophy has not been described in Machado-Joseph disease; (3) dentato-rubro-pallido-luysian degeneration [11, 16]; (4) some hereditary multisystemic degenerations with an unusual combination of cerebellipetal, dentato-rubral, and nigro-subthalamo-pallidal degenerations but with only slight changes in the inferior olives and the cerebellar cortex and none in the retina [19]; and (5) optico-cochleo-dentate atrophy [6, 22] because of lack of deafness and the mode of inheritance.

Our family is difficult to classify within the heterogeneous group of autosomal dominant cerebellar ataxias. Using a recent classification [27], we include for the present time this disorder in the "group of dominant ataxia, other types; subgroup with retinal degeneration".

Since our family is genetically distinct from SCA1 and SCA2 and probably also from MJD, another genetic locus must exist that is responsible for the retinal-cerebellar atrophy in this family. In current linkage studies we are using highly informative microsatellite markers throughout the genome (genome-wide search) to locate the disease-causing gene. In SCA1 as well as in other neurological diseases it has been demonstrated that the anticipation phenomenon is due to an incremental expansion of a CAG repeat. Therefore, we are preferentially testing available trinucleotide repeat markers in the genome-wide search.

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References

1. Auburger G, Diaz GO, Capote RF, Sanchez SG, Perez MP, del Cueto ME, Meneses MG, Farrall M, Williamson R, Chamberlain S, Baute LH (1990) Autosomal dominant ataxia: genetic evidence for locus heterogeneity from a Cuban Founder-effect population. Am J Hum Genet 46: 1163–1177
2. Bergstedt M, Johansson S, Müller R (1962) Hereditary spastic ataxia with central retinal degeneration and vestibular impairment. A clinical report on a family. Neurology 12: 124–132
3. Björk A, Lindblom U, Wadensten L (1956) Retinal degeneration in hereditary ataxia. J Neurol Neurosurg Psychiatry 19: 186–193
4. Chamberlain S, Shaw J, Rowland A, Wallis J, South S, Nakamura Y, von Gabain A, Farrall M, Williamson R (1988) Mapping of mutation causing Friedreich's ataxia to human chromosome 9. Nature 334: 248–250
5. Duinkerke-Eerola KU, Cruysberg JRM, Deutman AF (1980) Atrophic maculopathy associated with hereditary ataxia. Am J Ophthalmol 90: 597–603

6. Ferrer I, Campistol J, Tobena L, Cusi V, Galofré E, Prat J (1987) Dégénérescence systématisée optico-cochléo-dentelée. J Neurol 234: 416–420
7. Foster JB, Ingram TTS (1962) Familial cerebro-macular degeneration and ataxia. J Neurol Neurosurg Psychiatry 25: 63–68
8. Fowler HL (1984) Machado – Joseph – Azorean disease. A ten-year study. Arch Neurol 41: 921–925
9. Gatti R.A, Berkel I, Boder E, Braedt G, Charmley P, Concannon P, Ersoy F, Foroud T, Jaspers NG, Lange K, Lathrop GM, Leppert M, Nakamura Y, O'Connell P, Paterson M, Salser W, Sanal O, Silver J, Sparkes RS, Susi E, Weeks DE, Wei S, White R, Yoder F (1988) Localization of an ataxia-telangiectasia gene to chromosome 11q22–23. Nature 336: 577–580
10. Gispert S, Twells R, Orozco G, Brice A, Weber J, Heredero L, Scheufler K, Riley B, Allotey R, Nothers C, Hillermann R, Lunkes A, Khati C, Stevanin G, Hernandez A, Magarino C, Klockgether T, Durr A, Chneiweiss H, Enczmann J, Farrall M, Beckmann J, Mullan M, Wernet P, Agid Y, Freund H-J, Williamson R, Auburger G, Chamberlain S (1993) Chromosomal assignment of the second locus for autosomal dominant cerebellar ataxia (SCA2) to chromosome 12q23–24.1. Nature Genet 4: 295–299
11. Goto I, Tobimatsu S, Ohta M, Hosokawa S, Shibasaki H, Kuroiwa Y (1982) Dentatorubro-pallidoluysian degeneration: clinical, neuro-ophthalmologic, biochemical, and pathologic studies on autosomal dominant form. Neurology 32: 1395–1399
12. Halsey JH Jr, Scott TR, Farmer TW (1967) Adult hereditary cerebello-retinal degeneration. Neurology 17: 87–90
13. Hamilton SR, Chatrian G-E, Mills RP, Kalina RE, Bird TD (1990) Cone dysfunction in a subgroup of patients with autosomal dominant cerebellar ataxia. Arch Ophthalmol 108: 551–556
14. Harding AE (1982) The clinical features and classification of the late onset autosomal dominant cerebellar ataxias. A study of 11 families, including descendants of "the Drew family of Walworth". Brain 105: 1–28
15. Harding AE (1984) The hereditary ataxias and related disorders. Clinical Neurology and Neurosurgery Monographs. Churchill Livingstone, Edinburgh
16. Iizuka R, Hirayama K, Maehara K (1984) Dentato-rubro-pallido-luysian atrophy: a clinico-pathological study. J Neurol Neurosurg Psychiatry 47: 1288–1298
17. Lazzarini A, Zimmerman TR, Johnson WG, Duvoisin RC (1992) A 17th-century founder gives rise to a large North American pedigree of autosomal dominant spinocerebellar ataxia not linked to the SCA1 locus on chromosome 6. Neurology 42: 2118–2124
18. Martin J-J (1970) Contribution à l'étude de l'anatomie du thalamus et de sa pathologie au cours des maladies dégénératives dites abiotrophiques. Thèse d' agrégation de l' Enseignement supérieur en Sciences Neurologiques. Acta Neurol Belg 70: 5–212
19. Mizutani T, Oda M, Abe H, Fukuda S, Oikawa H, Kosaka K (1983) Hereditary multisystemic degeneration with unusual combination of cerebellipetal, dentato-rubral, and nigro-subthalamo-pallidal degenerations. Clin Neuropathol 2: 147–155
20. Morton NE, Lalouel J-M, Jackson JF, Currier RD, Yee S (1980) Linkage studies in spinocerebellar ataxia (SCA). Am J Med Genet 6: 251–257
21. Neetens A, Martin J-J, Libert J, Van Den Ende P (1990) Autosomal dominant cone-dystrophy-cerebellar atrophy (ADCoCA) (modified ADCA Harding II). Neuro-ophthalmology 10: 261–275
22. Nyssen R, van Bogaert L (1934) La dégénérescence systématisée optico-cochléo-dentelée. Rev Neurol (Paris) 2: 321–345
23. Orr H T, Chung M Y, Banfi S, Kwiatkowski T J Jr, Servadio A, Beaudet A L, McCall AE, Duvick LA, Ranum LP Zoghbi HY (1993) Expansion of an unstable trinucleotide CAG repeat in spinocerebellar ataxia type 1. Nature Genet 4: 221–226
24. Rich SS, Wilkie P, Schut L, Vanve G, Orr HT (1987) Spinocerebellar ataxia: localization of an autosomal dominant locus between two markers on human chromosome 6. Am J Hum Genet 41: 524–531
25. Stanescu B, Evrard P, Michiel SJ, Lyon G (1980) Electroretinographic changes in a case of spino-cerebellar degeneration (SCD). Metab Pediatr Ophthalmol 4: 221–223
26. Sternberger LA (1986) Immunocytochemistry, 3rd edn. Wiley and Sons, New-York
27. Subramony SH, Currier RD (1991) The classification of familial ataxias. Handb Clin Neurol 60: 271–284
28. Takiyama Y, Nishizawa M, Tanaka H, Kawashima S, Sakamoto H, Karube Y, Shimazaki H, Soutome M, Endo K, Ohta S, Kagawa Y, Kanazawa I, Mizuno Y, Yoshida M, Yuasa T, Horikawa Y, Oyanagi K, Nagai H, Kondo T, Inuzuka T, Onodera O, Tsuji S (1993) The gene for Machado-Joseph disease maps to chromosome 14q. Nature Genet 4: 300–304
29. Van Broeckhoven C, Backhovens H, Cruts M, De Winter G, Bruyland M, Cras P, Martin J-J (1992) Mapping of a gene predisposing to early-onset Alzheimer's disease to chromosome 14q24.3. Nature Genet 2: 335–339
30. Verougstraete C, Toussaint D (1973) Dégénérescence tapéto-rétinienne avec ataxie cérébelleuse: étude clinique de plusieurs membres d' une même famille. Bull Soc Belge Ophtalmol 164: 285–295
31. Weiner LP, Konigsmark BW, Stoll J Jr, Magladery JW (1967) Hereditary olivopontocerebellar atrophy with retinal degeneration. Report of a family through six generations. Arch Neurol 16: 364–376
32. Yuasa T, Ohama E, Harayama H, Yamada M, Kawase Y, Wakabayashi M, Atsumi T, Miyatake T (1986) Joseph's disease: clinical and pathological studies in a japanese family. Ann Neurol 19: 152–157
33. Zoghbi HY, Sandkuyl LA, Ott J, Daiger SP, Pollack M, O'Brien WE, Beaudet AL (1989) Assignment of autosomal dominant spinocerebellar ataxia (SCAI) centromeric to the HLA region on the short arm of chromosome 6, using multilocus linkage analysis. Am J Hum Genet 44: 255–263