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A clinicogenetic analysis of six Indian spinocerebellar ataxia (SCA2) pedigrees
The significance of slow saccades in diagnosis

Noshir Wadia,[1] Joanna Pang,[2] Joy Desai,[1] Ami Mankodi,[1] Margi Desai[1] and Susan Chamberlain[2]

[1]*The Department of Neurology, Jaslok Hospital and Research Centre, Bombay, India and* [2]*Hereditary Ataxia Research Group, Molecular Genetics, Division of Biomedical Sciences, Imperial College School of Medicine, London, UK*

Correspondence to: Dr Wadia, Department of Neurology, Jaslok Hospital and Research Centre, 15 G. Deshmukh Marg, Bombay 400 026, India

Summary
Clinical revaluation and genetic analysis of six Indian pedigrees, segregating autosomal dominant cerebellar ataxia, slow saccades and peripheral neuropathy, has been undertaken, and expansion at the spinocerebellar ataxia 2 (SCA2) locus was confirmed in 14 affected family members. These families became available from 31 phenotypically similar families seen over the years. In common with other neurodegenerative disorders resulting from expansion of a CAG trinucleotide repeat motif, an inverse correlation between repeat size and age at onset and severity is observed, although the size range (36–45 repeat units) for the expanded alleles is comparatively limited. Saccadic velocity was reduced in all our patients, even in the early stages of the disease. The observation of slow saccades in affected individuals has been proposed previously as an important diagnostic criterion serving to distinguish the SCA2 phenotype. This is now confirmed in a retrospective study of the clinical literature, facilitated by the cloning of the SCA2 gene and the subsequent genetic analysis of families segregating this phenotype. We therefore argue that the clinical appraisal of 'ophthalmoplegia' be subject to more precise definition, as differentiation between the various types of ocular dysfunction can be an important adjunct to diagnosis.

Keywords: ataxia; slow saccades; SCA2; CAG trinucleotide repeat; ophthalmoplegia

Abbreviations: ADCA = autosomal dominant cerebellar ataxia; SCA = spinocerebellar ataxia

Introduction
Since Friedreich originally reported a unique form of 'Hereditare ataxie' in 1861 and 1863, the literature has essentially comprised a series of clinicopathological descriptions of white Caucasian families, whose members exhibited cerebellar ataxia with a variety of neurological signs resulting from associated neuronal degenerations. Collectively, these disorders have been designated as 'spinocerebellar degenerations' or 'hereditary ataxias'. In landmark monographs covering a hundred years, Greenfield (1954) and Harding (1984) comprehensively reviewed the published information underscoring the clinical variation and pathological differences observed between the families.

Prominent amongst these disorders are the autosomal dominant cerebellar ataxias (ADCAs), characterized pathologically by olivopontocerebellar atrophy. In addition to the cerebellar ataxia, a number of additional, but variable, signs appear as a result of neuronal degeneration in the spinal cord, posterior root ganglia, brainstem, basal ganglia, substantia nigra and macula, leading to inter- and intrafamilial clinical heterogeneity. Classification systems derived from clinical and pathological observations have, however, largely failed in their objective to provide a reliable diagnostic basis for the individual disorders, primarily because precise clinical distinction is not always possible.

In 1971, Wadia and Swami described nine Indian families exhibiting a 'new form of spinocerebellar degeneration different from the previously described familial ataxias of the West', the consistent distinguishing sign being the slow saccadic eye movements. Pneumoencephalography demonstrated cerebellar and pontine atrophy, and electromyography showed patterns of chronic denervation in the limb muscles. Subsequent electro-oculography indicated a reduction in saccadic velocity and showed normal pursuit movements (Kulkarni and Wadia, 1975). Four autopsy examinations, sural nerve biopsies and more detailed electromyography revealed degeneration in the cerebellum,

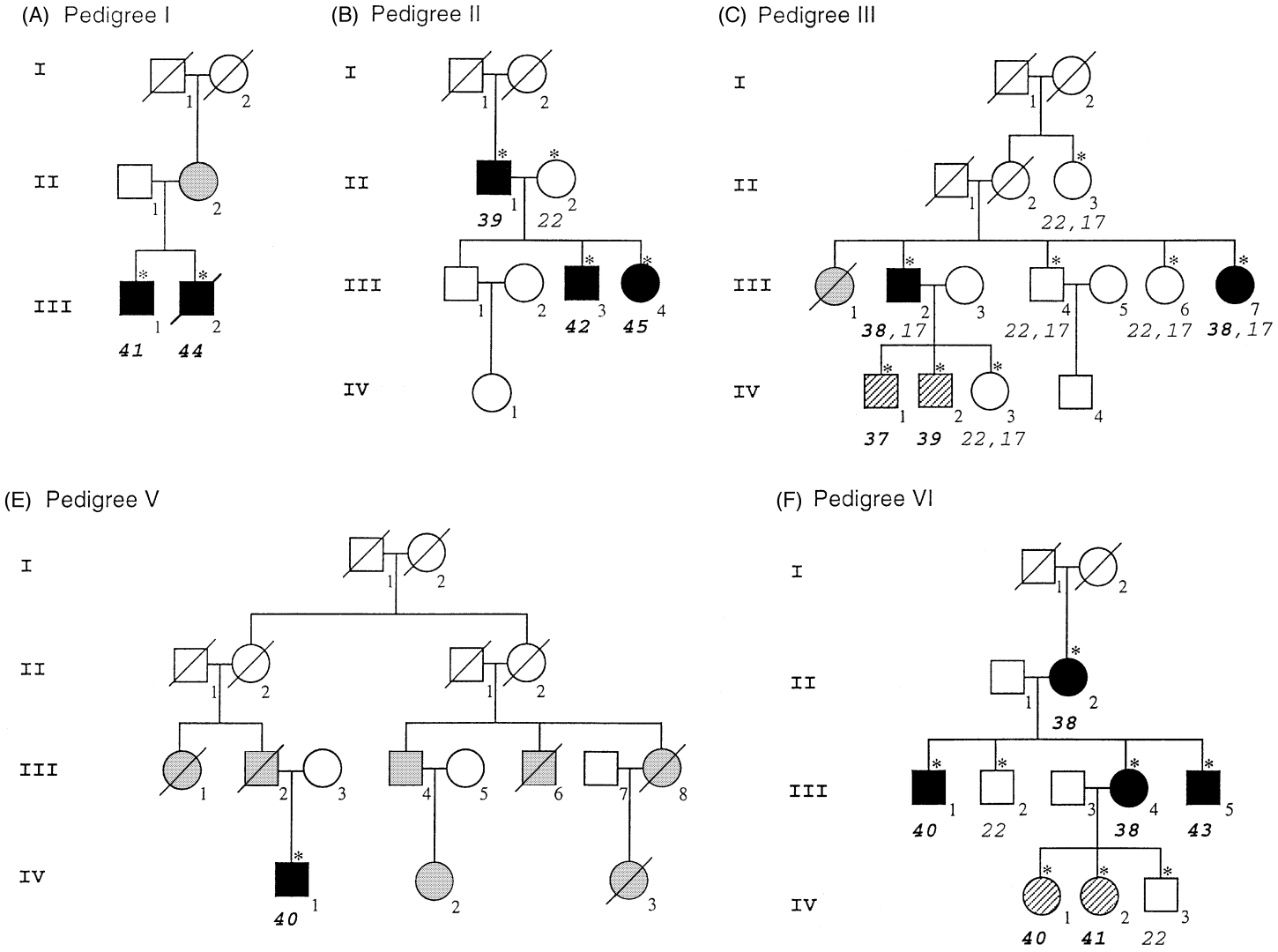

Fig. 1 (**A**–**F**) Investigation of six Indian families segregating ADCA and slow saccades for expansion at the SCA2 locus. Allele sizes are indicated in italics; expanded alleles are in bold. For affected individuals, the normal allele comprises 22 repeat units unless stated. Homozygosity for alleles comprising 22 repeat units for unaffected individuals should also be assumed, unless stated otherwise. Individuals are represented (squares for males and circles for females) as follows: affected according to the examination (black-filled symbols); unaffected according to the examination (open symbols); affected by history (grey-filled symbols); and asymptomatic individuals (normal neurological status in 1996/7) with expanded alleles (hatched symbols).

pons, anterior horn cells and dorsal root ganglia, and 'dying-back' sensorimotor neuropathy (Wadia, 1977, 1984; Wadia *et al.*, 1980). This led to the acceptance of the disease as an identifiable phenotype (Duvoisin, 1984; Plaitakis, 1987; Currier and Subramony, 1993). CT and MRI scans showed the olivopontocerebellar atrophy more vividly during life (Wadia, 1991, 1993*a*).Within the last decade, genetic analysis has led to the construction of a classification system based on either the chromosomal assignment of a disease locus or the identification of gene mutation, the latter facilitating accurate genetic counselling of families affected by these disorders. In this report, we demonstrate expansion at the spinocerebellar ataxia 2 (SCA2) locus in six unrelated Indian families segregating ADCA with slow saccades. This observation has prompted a critical review of the literature, to investigate the incidence of the eye-movement anomaly in pedigrees for which molecular analysis has confirmed a diagnosis of SCA2, leading us to comment on the presence of this feature as a primary diagnostic criterion and on the definition of ophthalmoplegia in affected individuals.

Methods

Patients

Thirty-one Indian families, whose members present with a slowly progressive cerebellar ataxia and show slow saccadic eye movements on examination, have been under the care of one of us (N.W.) since 1962. Of the 627 family members, 135 have been personally examined, and 53 individuals have

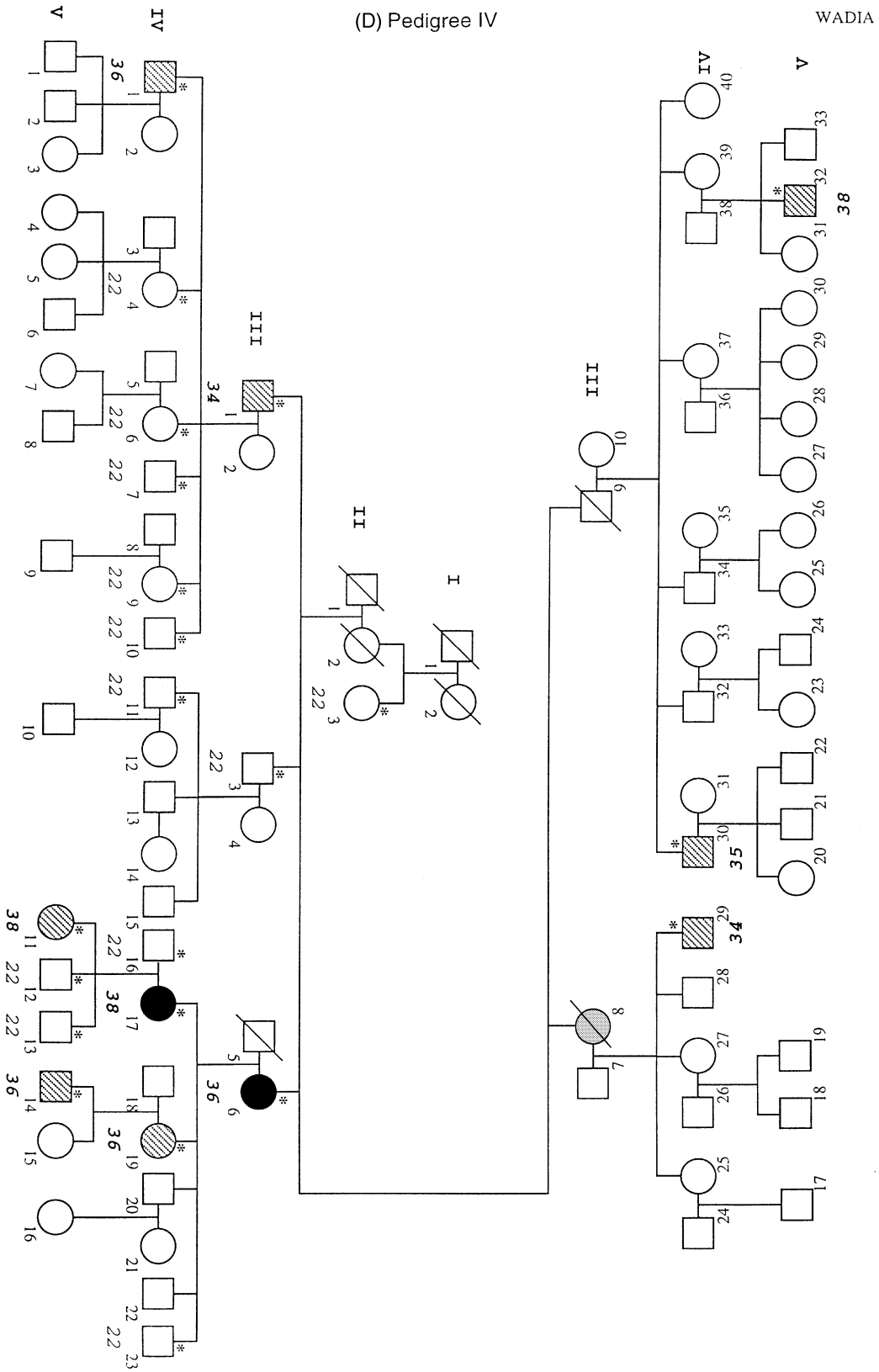
(D) Pedigree IV
WADIA
I
II
III
IV
V

Table 1 *Clinical disability scores*

Score	Symptoms
General	
<3	Mild
4–6	Moderate
7–10	Severe
10	Total disability
Cerebellar ataxia	
1	No symptoms, mild signs
2	Symptoms of gait ataxia, can walk unaided, no falls
3	Wide-based slow gait, needs slight support, occasional falls
4	Needs full support to walk, frequent falls
5	Wheelchair or bed bound
Eye movements	
1	Slow saccades just perceptible, no head-eye lag
2	Perceptible slow saccades, blinks, slight head-eye lag
3	Obvious slow saccades, blinks, head-eye lag, head jerks
4	Very slow saccades, blinks, head-eye lag, head jerks, needs Doll's eye manoeuvre to move eyes
5	Slight spontaneous eye movements, remarkable stare, head jerks, needs the Doll's eye manoeuvre to move eyes or terminal gaze paresis

been found to be affected. Careful questioning revealed that a further 30 individuals were thought to be affected by history. Previous publications have detailed the clinical profile in 29 of these families (Wadia and Swami, 1971; Wadia, 1977, 1984, 1991, 1993*a*; Wadia *et al*., 1980).

Members of six of these families (Fig. 1A–F) agreed to a clinical re-evaluation and DNA analysis after careful explanation of the reasons for, and the implications of, this study. An autosomal dominant pattern of inheritance was directly observed in Pedigrees II, IV and VI, and could be inferred by history in Pedigrees I and V. All six families appear unrelated, originating from geographically distinct locations in the country. Five are Hindus and one Muslim. Of the 251 individuals for whom information was available, clinical examination was carried out in 53 by N.W., to ensure consistency. Fourteen individuals were found to be affected at various stages of the disease. Of the other 198 members who could not be examined, nine were thought to be affected by history. The age at onset and the severity and duration of the ataxia until the point of examination (1996–7) was carefully ascertained. Disability was graded according to Table 1.

Investigations

To support the clinical diagnosis, a CT scan of the brain was performed in 10 patients and MRI in four cases. Electro-oculography, saccadic velocity measurements and electro-myography and nerve conduction studies were all performed in the same eight patients. The velocity of the horizontal saccade was measured after recording the horizontal eye movements on a full-field, DC-operated Ganzfeld electro-oculograph. The patient was asked to look at two LED lights which were alternately switched on and off. The lights are in a globe subtended at an angle of 30° with the patient sitting at the apex. Recording was made with Ag/AgCl disc electrodes placed on the outer and inner canthi of each eye. The data were recorded through an Evomatic 8000 Dantec recorder, and printed on strip paper. The saccadic velocity was manually calculated from the angle subtended and the rise time of the recorded curves.

Electrophysiological studies (EMG and nerve conduction velocities) were carried out on a Dantec Counterpoint, adopting standard procedures, and the results were compared with normal values established in our department. EMG was performed in several muscles of the upper and lower limbs. The motor conduction velocity was measured in the median, ulnar, peroneal and tibial nerves and the sensory conduction in the median, ulnar and sural nerves. In all the motor conduction velocity was measured in 26 nerves, and sensory action potentials in 43 nerves, of the eight patients. Visual and brainstem auditory evoked potentials were recorded in four patients.

To investigate the expansion of the SCA2 locus, blood samples were obtained from 51 members of the six families, including the 14 affected individuals, and DNA was extracted. PCR (polymerase chain reaction) amplification of the SCA2 locus, using primers flanking the CAG repeat motif, and analysis by polyacrylamide gel electrophoresis were performed as described by Pulst *et al*. (1996).

Results

Disease manifestations

Cerebellar ataxia and slow saccadic eye movements, with normal pursuit movements were seen in all 14 cases examined, i.e. from onset to very late stages (Fig. 2A). The initial symptom in all patients was difficulty in walking due to imbalance. On examination, an ataxic gait, limb incoordination, intention tremor and dysarthria of differing grades of disability were found, ultimately leading to decubitus.

The eye disorder, which appeared simultaneously, was more subtle at the onset, only becoming apparent on examination; the patients were unaware of it. In six mildly affected individuals, a slowing of the horizontal command and random eye movements (saccades) was seen without any limitation of their range (Fig. 2A). In four moderately disabled patients, pre-saccadic blinks and compensatory jerks of the head to scan the surroundings were noted. A staring look due to absence of the small fixation saccades was noticed. In these individuals, the vertical saccades were also slow. When attempting to fixate on a target, the head and neck quickly turned towards the object and the eyes were seen to slowly lock on the target producing a clinically appreciable 'head–eye lag'. In four patients, severely disabled by an advanced stage of the disease, the eyes were more fixed with

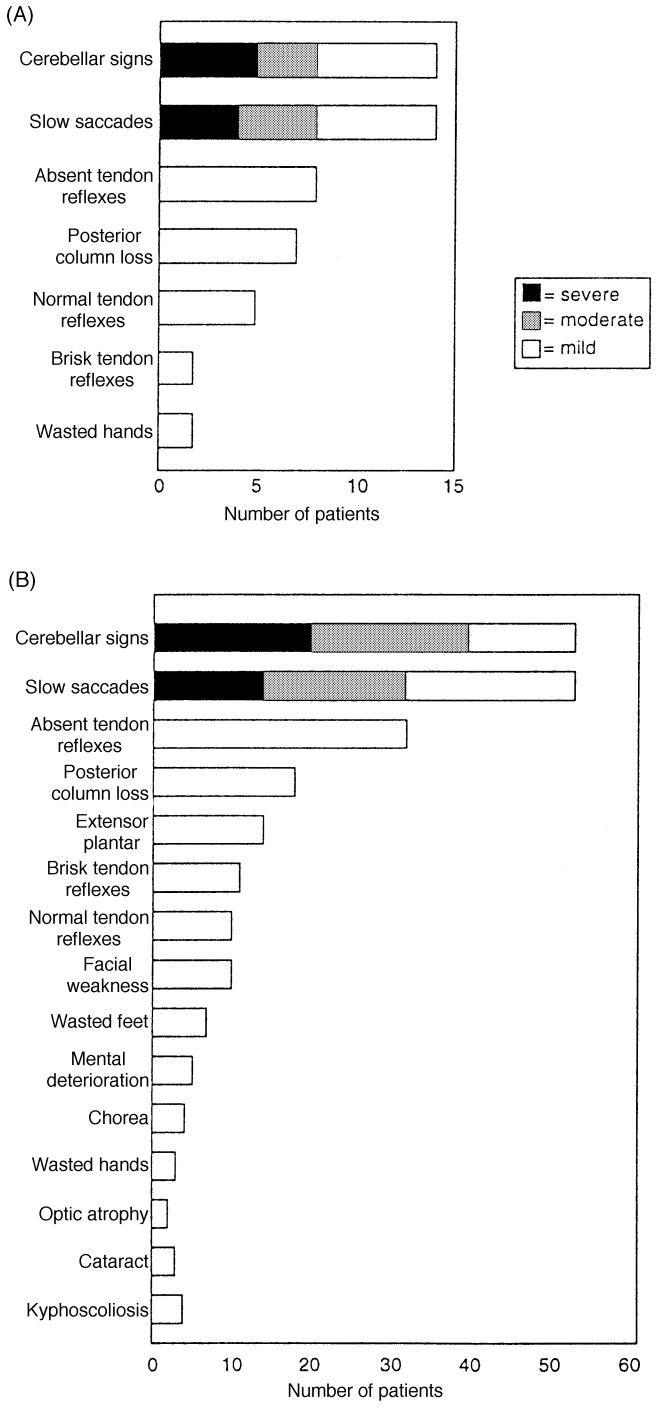

Fig. 2 Incidence of the clinical features observed in (**A**) the 14 affected members of Pedigrees I–VI and (**B**) the 53 members of the 31 pedigrees examined since 1962, indicating that cerebellar ataxia and slow saccades constitute the core features of the phenotype segregating in these families.

virtually no spontaneous or command-related movements. Yet, in three of them, the eyes could be moved through their full range of movements by the 'oculocephalic manoeuvre'. In the most severely affected patient, a bilateral restriction of lateral gaze was seen. The analysis of these patients was done at their last examination. In two patients who were repeatedly examined over the years, it was obvious that the fixed eyes of the severely affected were merely an advanced stage of slowing of the saccades, ultimately mimicking lateral gaze palsy which truly means binocular, conjugate limitation in amplitude. None of the patients complained of diplopia. Ptosis, squint, pupillary abnormality and nystagmus were not observed in any patient. The ocular slowing was noted to progress concomitantly with the cerebellar ataxia. However, in four individuals the ataxia was a little more remarkable than the ocular slowing, while the reverse was true in one. The compensatory head jerk or thrust, of which the patient is not aware, is a useful sign indicating a slowing of the saccade. Indeed once made aware of this sign, an alert relative can identify affected members in whom the disease had not been suspected.

The other significant clinical signs were absence of deep tendon reflexes (57%) and diminished vibration sense (50%). In general, the upper limb reflexes were more depressed than those of the lower limbs, and the ankle jerk more than the knee. In the early stage of the disease these deep tendon reflexes were noted to be normal, with the exception of one patient in whom they were brisk. On re-evaluation, as the disease progressed, these reflexes were noted to disappear, including the brisk ones.

An analysis of the clinical manifestations in 53 members of 31 families, illustrating our total experience (Fig. 2B) showed that the dominant clinical signs were cerebellar ataxia and slow ocular saccades in all the patients, as described earlier. The other signs were less constant. The tendon reflexes were mostly abnormal. In the majority, they were absent. Usually, the normal or brisk tendon reflexes seen when the patient was first examined disappeared as the disease progressed. Impairment of the vibration sense in the lower limbs was the next most common sign, followed by plantar extensor response in 17 patients. Distal limb wasting was very occasionally seen. Chorea was evident in only four severely affected patients, two of whom belonged to the same family. Mental changes were infrequent, and appreciable only at an advanced stage of the disease. The facial weakness was mild, and optic atrophy was seen in only two patients. It appears that in our Indian patients the frequency of associated signs, except for absent tendon reflexes and posterior column disorder, is low compared with the constant manifestation of cerebellar ataxia and the slow saccades. Indeed, we did not see these signs, except for wasted hands in one patient, in the six families genetically analysed here. We have not come across any cardiac disorder. Cataracts at a young age were seen in the families examined early in the study, but not since.

Age at onset

The mean age at onset of the disease (± SD) was 27.5 ± 8.3 years (n = 14; range 16–48 years). An analysis of the age at onset in the affected parent and children was possible in four families. The disease manifested significantly earlier in

Table 2 *Clinical and genetic data for the 14 affected members of the six Indian pedigrees investigated for expansion at the SCA2 locus*

Patient	Age at onset (years)	Disease duration (years)	Cerebellar signs*	Slow saccades*	Tendon reflexes	Posterior column loss	Wasted hands	$(CAG)_n$ repeats
Pedigree I								
III.1	33	6	1	1	N	–	–	41/22
III.2	21	17	5	4	A	+	–	44/22
Pedigree II								
II.1	48	13	3	2	A	+	–	39/22
III.3	23	6	1	3	N	–	–	42/22
III.4	18	7	4	3	A	–	–	45/22
Pedigree III								
III.2	31	10	1	1	N	+	–	38/17
III.7	23	8	2	2	A	+	–	38/17
Pedigree IV								
III.6	35	16	3	3	N	+	–	36/22
IV.17	22	13	3	3	A	+	–	38/22
Pedigree V								
IV.1	25	5	1	1	B	–	–	40/22
Pedigree VI								
II.2	36	34	5	5	A	+	+	38/22
III.1	23	21	5	4	A	+	–	40/22
III.4	32	3	1	1	N	–	–	38/22
III.5	16	15	4	4	A	–	–	43/22

Each patient has been scored for the degree of clinical disability (*) associated with the cerebellar ataxia and eye movements as described in Table 1. The tendon reflexes are indicated as normal (N), absent (A) or brisk (B). The number of repeat units detected for both the affected and normal chromosomes segregating in the affected individuals is given.

Table 3 *Velocity of eye movements in eight patients and one unaffected relative*

Pedigree/ Patient	Velocity (°/s)	Eye movement disability score
I/III.1	263 ± 17.5	1
II/III.3	102.7 ± 12.4	3
II/III.4	67 ± 20	3
IV/IV.17	83.1 ± 20	3
V/IV.1	192.8 ± 23.8	1
V/IV.2	103 ± 25	3
VI/III.4	162.2 ± 23.9	1
VI/III.5	100.2 ± 12.4	4
VI/III.2*	322.5	0

*Unaffected member of Family VI. Mean saccadic velocity in control subjects = 304.6 ± 24.1°/s. Mean saccadic velocity in patients = 127.7 ± 21.9°/s.

the children than in their affected parents. The mean age at onset in children was 22.7 ± 4.4 years (n = 8; range 16–32 years) and in the parents 38.5 ± 5.5 years (n = 4; range 35–48 years). The greatest difference was 30 years (Pedigree II) and the least was 4 years (Pedigree VI) with a mean difference of 15.7 ± 8.1 years (Table 2).

Severity of the disease

The duration of the disease ranged from 3 to 34 years (mean ± SD, 12.4 ± 7.8 years) (Table 2). The severity of the disease was judged by the degree of disability and the time taken to reach that stage. Figure 3 shows this in the parent–child pairs of three families examined on two occasions. As can be seen, the children were more severely affected at a much younger age than their respective parents. In Pedigree II (Fig. 3A and Table 2) the disability score of the parent (II.1) was 5 after 13 years from onset of the disease, while it was 7 after only 7 years in his child (III.4). The biggest difference in the age at onset (30 years) was also noted in this parent–child pair. Pedigree IV (Fig. 3B) shows that the child (IV.17) deteriorated by one score while the mother (III.6) did not worsen at all during this 3-year period of evaluation. In Pedigree VI (Fig. 3C), one sibling (III.1) progressed to the disability score of nine in 21 years while another (III.5) reached the score of eight quicker, in only 15 years. The latter was the youngest affected individual, with onset at 16 years. The mother's (II.2) disease progressed more slowly reaching a state of decubitus (score 10) after 34 years. Two patients died ~1 year after their last examination, one (Pedigree I/III.2) a little more than 17 years after onset of the disease at 21 years, and another (Pedigree VI/II.2) died 35 years after a later onset of ataxia at the age of 36 years.

Investigations

CT and MRI confirmed cerebellar and pontine atrophy in all 14 cases.

Electro-oculography revealed significant slowing of the saccadic velocity compared with the normal control mean velocity of 304.6 ± 24.1°/s (Table 3). It ranged from marked

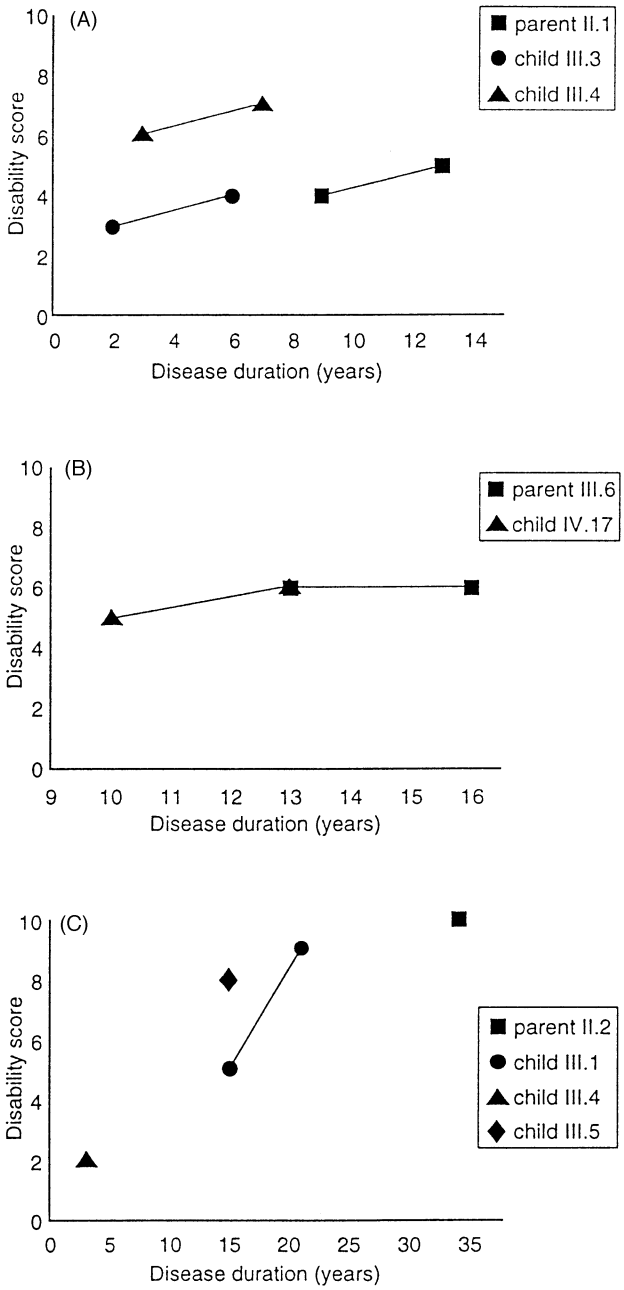

Fig. 3 Relationship between total disability score and disease duration in the affected parents and offspring of Pedigrees II (**A**), IV (**B**) and VI (**C**). The maximum disability score (decubitus) is 10.

slowing (67 ± 20°/s) with a disability score of 3 to slight but clinically perceptible yet significant slowing (263 ± 17.5°/s) with a score of 1. In addition, the reduction in velocity in individual patients corroborated somewhat closely with our clinical disability score of eye movements.

Electrophysiological examination (Table 4) showed evidence of a sensory neuropathy. The sensory nerve action potentials were significantly attenuated in all the median and ulnar nerves and in two sural nerves with normal sensory conduction velocities. With the exception of one patient (VI/III.5), the EMG and all parameters of motor nerve conduction were within normal limits. The study thus showed that the sensory nerves in the upper limbs were earlier and more affected than those in the lower limbs. Further, it revealed that the electrophysiological examination is in advance of the clinical one in detecting the sensory neuropathy, as in two patients the tendon reflexes were normal and in one brisk, when the sensory nerve action potentials were significantly attenuated, especially in the upper limbs.

The visual and brainstem auditory evoked potentials were normal in all four in whom they were recorded.

Characterization of the expansion at the SCA2 locus

Twenty-six of the 44 family members for whom results were obtained exhibited expansion at the SCA2 locus, including the original 14 affected individuals and 12 asymptomatic individuals with normal neurological status when last examined (1996–7) (Fig. 1). Allelic expansion detected in the patients ranged from 36 to 45 repeats (Table 2; Fig. 4) and their age at onset from 16 to 48 years. For the 11 young asymptomatic individuals (7–37 years), the expansion size ranged from 34 to 41 repeat units. The remaining asymptomatic individual, a 60-year-old man, who showed no evidence of a neurological deficit when last examined in 1996, exhibited the smallest expansion (34 repeats) detected in these pedigrees to date. Polymorphism for the non-disease chromosome segregating in the affected individuals was remarkably low, with 24 chromosomes having 22 repeat units and just two chromosomes with 17 repeat units.

Although the overall relationship between age at onset and size of the expansion (Fig. 5) is not as marked as that reported for other SCA loci, primarily due to the limited size range of expanded alleles, five of the six pedigrees show clear evidence of an inverse correlation. This is particularly evident in Pedigree VI, where transmission of the disease allele from the mother II.2 (onset at 36 years; repeat length, $n = 38$) to her two affected sons is accompanied by a decrease in age at onset and an increase in the number of repeat units: III.1 (onset at 23 years; $n = 40$) and III.5 (onset at 16 years; $n = 43$). Stable transmission of the disease allele to the affected daughter, III.4, is observed; the age at onset in this individual was similar to that for her mother. Contraction of the expansion was detected in a single individual; a reduction in the number of repeat units from 38 to 37 was observed in the transmission of the disease allele from individual III.2 in Pedigree III to his asymptomatic son IV.1. As the latter is young (11 years), it is not possible to comment on the consequence of this contraction on the age at onset at this time.

No evidence for parental bias was evident from this study. However, the greatest increase was detected following transmission of the affected allele from individual II.1 (39 repeats) to his affected daughter III.4 (45 repeats) in Pedigree II, accompanied by a reduction of 30 years in the age at

Table 4 *Results of sensory action potential examination*

Pedigree/ Patient		Median nerve		Ulnar nerve		Sural nerve		Tendon reflexes
		Potential amplitude ($n \geqslant 10$ μv)	Conduction velocity ($n \geqslant 47$ m/s)	Potential amplitude ($n \geqslant 8$ μv)	Conduction velocity ($n \geqslant 47$ m/s)	Potential amplitude ($n \geqslant 5$ μv)	Conduction velocity ($n \geqslant 41$ m/s)	
I/III.1	R	5	81	5	72	35	55	N
	L	7	71	5	74	38	53	
II/III.3	R	9.4	59	5.3	61	17.5	56	N
	L	14.9	59	8.7	58	ND	ND	
II/III.4	R	2.5	52	< 1	46	15	55	A
	L	ND	ND	ND	ND	15	53	
IV/IV.17	R	2.5	42	2	48	10	47	A
	L	ND	ND	ND	ND	10	55	
V/IV.1	R	3.3	ND	2.3	ND	ND	ND	B
	L	4.3	ND	2.9	ND	19.5	ND	
V/IV.2	R	2.2	56	2.4	55	6	50	A
	L	3	56	2.5	50	6	52	
VI/IV.4	R	10	55	7.6	66	20	57	N
	L	17	52	10	59	20	62	
VI/III.5	R	3.6	62	2.6	56	4	48	A
	L	3	59	2.6	65	3.9	52	

L = left; R = right; N = normal; A = absent; B = brisk; ND = not done.

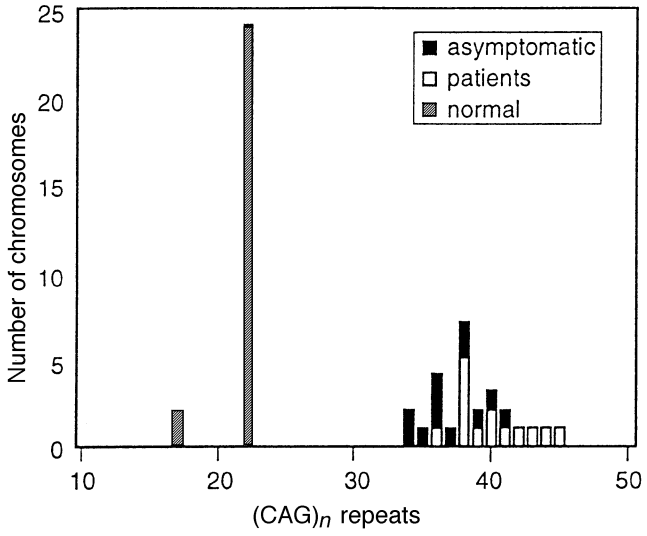

Fig. 4 Distribution of allele sizes observed for the disease and normal chromosomes segregating in the affected individuals, according to the number (*n*) of CAG repeat units present.

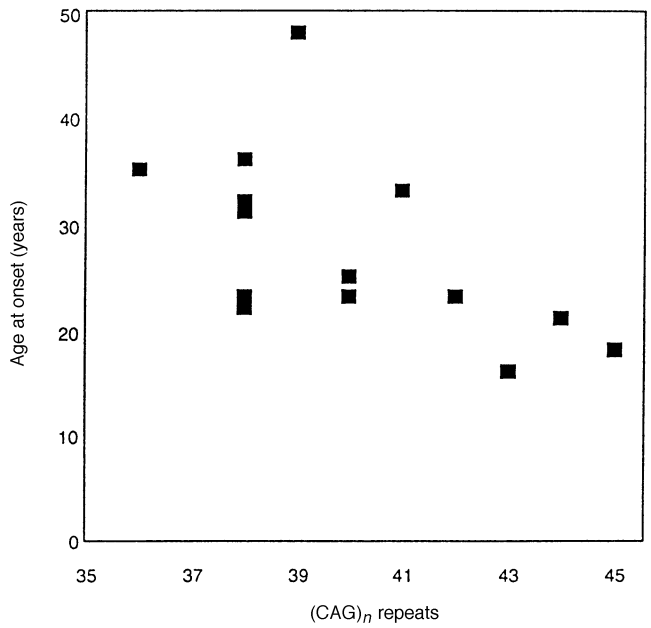

Fig. 5 Inverse correlation between age at onset and CAG repeat length in the 14 affected members of Pedigrees I–VI investigated for expansion at the SCA2 locus.

onset. Correlation between increasing expansion size and severity of the disease seemed evident in all families, although the relatively small number of subjects precluded a definitive answer through statistical analysis.

Discussion

The clinical diagnosis in the six families who agreed to the re-evaluation and DNA analysis was consistently based on finding progressive symmetrical cerebellar ataxia and slow saccadic eye movements. More than half of these patients had absent tendon reflexes, vibration sense was reduced in 50%, and wasting of the hands in one, at the stage when we examined them (Table 2). Despite increasing reduction in the velocity of the saccade as the disease advanced, there was no limitation in the range of movement; it was limited only at a later stage of the disease. Other associated signs like the extensor plantar response, facial weakness, wasted feet, mental deterioration, chorea and optic atrophy recorded in the first nine families of Wadia and Swami (1971) were not found in this group and were seen less frequently in the

subsequent families reported by Wadia (1977, 1984, 1991, 1993*a*) (and see Fig. 2B). Hence, these did not form the core signs of the disease in our patients. It was the slow saccade and, to a lesser extent, depressed tendon reflexes which consistently identified this sub-phenotype of ADCA1.

The observation of progressive cerebellar ataxia and slow eye movements is not a new one. In 1933, Mass and Scherer described a case, albeit sporadic, of a German lady aged 33 years with severe cerebellar ataxia of 5 years duration in whom they found absent tendon reflexes and extensor plantar responses. 'Eye movements in all directions were full but slow when the patient looked spontaneously or on command to one side'. There was no nystagmus. Caloric stimulation and rotation caused deviation of the eyes to one side without nystagmus. Multiple sclerosis was initially diagnosed, but 5 years later, when she died, autopsy revealed olivopontocerebellar degeneration and severe demyelination of the posterior roots and columns. This could be the first reported case of SCA2, well before the arrival of molecular genetics. Somewhat similar single autosomal dominant families were reported by Sigwald *et al*. (1963, 1967) from France, and by Kini and Venugopal (1967) from India.

However, it was Wadia and Swami (1971) who first drew attention to the separate clinical identity of this type of ataxia amongst the then recognized ADCAs and to the greater prevalence or recognition of this disorder in India. In his subsequent publications, Wadia reported more families (1977, 1984, 1991, 1993*a*) and referred to those seen by others in India (Kini and Venugopal, 1967; R. S. Wadia *et al*., 1976) and in different parts of the world (Mass and Scherer, 1933; Garcin and Man, 1958; Gerstenbrand and Weingarten, 1962; Sigwald *et al*., 1963, 1964; Starkman *et al*., 1972; Singh *et al*., 1973; Ozawa *et al*., 1974; Sears *et al*., 1975; Koeppen and Hans, 1976; Sharpe, 1976; Zee *et al*., 1976*a*, *b*; Koeppen *et al*., 1977; Murphy and Goldblatt, 1977; Cambier *et al*., 1978; Avanzini *et al*., 1979; Kanehisa *et al*., 1979; Lai and Hung, 1979; Oppenheimer, 1980; Rondot *et al*., 1983; Plaitakis, 1987; Orozco Diaz *et al*., 1989, 1990). Some of these reports stressed the slow saccadic eye movements, and many compared their cases with those reported in 1971 by Wadia and Swami (Starkman *et al*., 1972; Singh *et al*., 1973; Ozawa *et al*., 1974; Koeppen and Hans, 1976; Murphy and Goldblatt, 1977; Avanzini *et al*., 1979; Lai and Hung, 1979; Rondot *et al*., 1983; Plaitakis, 1987). Autopsies, whenever performed, showed olivopontocerebellar degeneration.

The last of these (then genetically unmapped) families came from Cuba (Orozco Diaz *et al*., 1989, 1990). The consistent clinical feature noted in these patients, besides a progressive cerebellar ataxia, was slowing of ocular saccades and ophthalmoplegia. Autopsy examinations performed in some of these patients invariably revealed olivopontocerebellar degeneration. The commendable epidemiological survey by Orozco Diaz *et al*. (1989, 1990) focused on the localization of these families to one district (Holguin) in Cuba and the 'founder effect' linking all these families. However, they failed to review the earlier global reports of similar families. Currier, who later personally examined some of these Cuban patients, maintained that they were phenotypically identical to those from India described by Wadia (Currier and Subramony, 1993). Wadia has always maintained that careful evaluation of the ocular signs to distinguish slow saccades from other ophthalmoplegias in a patient/family with cerebellar ataxia could with reasonable confidence identify this sub-type of ADCA1 clinically (Wadia and Swami, 1971; Wadia, 1977, 1984, 1991, 1993*a*). Though this view gained acceptance in some classifications (Duvoisin, 1984; Plaitakis, 1987; Currier and Subramony, 1993), its specificity remained to be proven.

All this was before genetic analysis became possible and prior to assignment of a second ADCA1 locus (SCA2) to chromosome 12q23–24.1 by Gispert *et al*. (1993) in the Cuban kindred mentioned above. The mapping of this disease gene prompted an investigation of the Indian families. At that time, although we were able to generate support for linkage to the chromosome 12 locus in pedigrees available for analysis, the study failed to achieve statistical significance (Wadia, 1993*b*). However, we have now demonstrated expansion at the SCA2 locus in six of the 31 Indian families exhibiting the 'core' phenotype of progressive cerebellar ataxia and slow saccades.

In the present study, pathological expansion at the SCA2 locus was demonstrated in all of the 14 affected individuals and 12 others who are so far unaffected. In common with other disorders involving triplet repeat expansions, the age at onset was younger and severity was greater amongst affected children than their respective parents. Further, a correlation between increasing expansion size and an earlier age at onset is also seen within these families. The greatest increase is detected following transmission of the affected allele from a father (39 repeats) to his daughter (45 repeats) in Pedigree II, and onset was 30 years earlier in the daughter.

It is evident from this study and others that the range of the expanded allele size for SCA2 is considerably more limited than that seen in other disorders characterized by triplet repeat expansion. Hence, relatively subtle differences in allele size can have a profound effect on the age at onset and severity of the disease. In a study of 32 SCA2 families, Cancel *et al*. (1997) reported that the relationship between the size of the CAG repeat and the age at onset was –3.24 years per CAG repeat. Due to the limited sample size, it was not possible to undertake formal regression analysis on the Indian families to investigate this correlation. However, it is clear that the relationship is more complex than previously stated. Reduction in the age at onset by 8 years without an accompanying alteration in the expanded allele size has been observed in Pedigree III. Conversely, interpretation of the data generated for Pedigree IV illustrates that the addition of only two repeat units can lead to a reduction in the age at onset by $>$12 years. However, it is notable that in this family, the individual (III.1) exhibiting the smallest expanded allele (34 repeats) detected in these pedigrees to date remains normal at the age of 60 years. In contrast, his affected sister

Table 5 *Literature review of the clinical and genetic analysis of SCA2 families*

Country	Reference	Families (*n*)	Patients examined (*n*)	Slow saccades (%)	Ophthalmo-plegia (%)	Genetic data
Austria	Gerstenbrand and Weingarten (1962)	1*	9(1†)		100	
	Lopes-Cendes *et al*. (1994)	1 (Austrian)*	32	81		Linkage
		1 (French)	18	94		
Cuba	Orozco Diaz *et al*. (1989, 1990)	53*	263(7†)	69	49	
	Gispert *et al*. (1993)	32*	450(11†)	?	?	Linkage
England	Giunti *et al*. (1995)	1	8	25	62.5	Linkage
France	Durr *et al*. (1995, 1996)	3	31(2†)	42	51	Linkage
	Imbert *et al*. (1996)	8	31	?	?	Gene
Germany	Burk *et al*. (1996, 1997)	3	27	81.5	58	Linkage
India	Wadia *et al*. (1997)	6	14	100		Gene
Italy	Filla *et al*. (1995)	1	6	100	75	Linkage
	Filla *et al*. (1996)	2	12	100	58.5	Linkage
Japan	Sanpei (1996)	1	57	?	?	Gene
	Sasaki *et al*. (1991), Ihara *et al*. (1994)	2	8(1†)	100		Linkage
Tunisia	Belal *et al*. (1994)	1	17		62	Linkage
USA	Geschwind *et al*. (1997)	5	16	92	60	Gene
	Starkman *et al*. (1972), Pulst *et al*. (1993)	1	17	65		Linkage
Multinational	Cancel *et al*. (1997)‡	32	111	56	52	Gene
	Pulst *et al*. (1996)§	9	?	?	?	Gene

*Same families reported. †Olivopontocerebellar degeneration at autopsy. ‡Includes families described by Durr *et al*. (1995, 1996), Burk *et al*. (1996, 1997) and Belal *et al*. (1994). §Includes families described by Lopes-Cendes *et al*. (1994), Starkman *et al*. (1972), Pulst *et al*. (1993, 1996) and Orozco Diaz *et al*. (1989, 1990).

(III.6), with onset at 35 years of age and a disease duration of 16 years, carries a marginally larger expansion, with just two additional repeat units. We would therefore agree with the conclusion drawn by Cancel *et al*. (1997), that the size of the pathological allele is not the only factor responsible for determining the age at onset, and that other factors, including genetic background, may also play a significant role.

Following the characterization of the SCA2 gene, ataxin-2 (Imbert *et al*., 1996; Pulst *et al*., 1996; Sanpei *et al*., 1996) a plethora of publications have appeared. Some describe the genetic analysis of new SCA2 families (Sasaki *et al*., 1991; Pulst *et al*., 1993; Belal *et al*., 1994; Ihara *et al*., 1994; Lopes-Cendes *et al*., 1994; Filla *et al*., 1995; Giunti *et al*., 1995; Sanpei *et al*., 1996; Burk *et al*., 1997), others the investigation of families already included in national and international patient cohorts (Burk *et al*., 1996; Durr *et al*., 1996; Filla *et al*., 1996; Cancel *et al*., 1997; Geschwind *et al*., 1997). The presence of slow saccades and 'ophthalmoplegia' represent an important feature in some or all members of the families described in these publications (Table 5). Although precise clinical description or definition of the ocular disorder is generally omitted from these reports, Giunti *et al*. (1995) have described it as 'restriction of saccade or pursuit eye movements'. No mention is made of the oculocephalic manoeuvre, head thrust, eye blinks or caloric stimulation which were found so useful in assessing our patients' eye-movement disorder. A variety of abnormal eye signs have been described in hereditary ataxias (Brown,1892; Greenfield, 1954; Zee *et al*., 1976*a*, *b*; Harding, 1984; Moschner *et al*., 1994; Baloh *et al*., 1997) and it is not always easy to distinguish them. It is likely that this oculomotor disorder can be misinterpreted as oculomotor apraxia or several other varieties of supranuclear ophthalmoplegia including gaze palsy (binocular, conjugate limitation in amplitude), especially at a later stage of the disease. Supranuclear ophthalmoplegias are usually asymptomatic. Further, absence of squint, ptosis and pupillary abnormality would rule out internuclear, nuclear and infranuclear ophthalmoplegias. Examination of less affected members would often reveal the saccadic slowing, indicating the nature of the fixed eyes in those more affected. Hence, a more precise clinical and, if required, oculometric appraisal should replace the general term 'ophthalmoplegia' used in recent classifications (Harding, 1984; Plaitakis, 1987; Hammans, 1996) and publications including those mentioned here. Refreshingly, Hurko (1997) in a recent editorial has appealed, especially to geneticists, to make 'detailed studies of oculomotor findings' regretting that 'current reports of linkage have provided only cursory clinical information about what exactly is being linked'.

We have observed that slowing of eye movements can be missed clinically when compensatory head jerks or eye blinking have not appeared or went unappreciated. Giunti *et al*. (1995) admitted that 'slow saccades may have been overlooked in some members of our SCA2 families who were examined in 1986'. This is also evident in some of the similar genetically unmapped families with slow saccades mentioned earlier (Singh *et al*., 1973; Koeppen and Hans, 1976; Murphy and Goldblatt, 1977; Oppenheimer, 1980). Records of affected members with cerebellar ataxia do not mention any ocular disorder as seen in the propositus or those of later generations. Conversely, it is likely that

'opthalmoplegia' and 'gaze palsy' mentioned in many publications of SCA2 represent the most severe manifestations of slow saccades. This is well illustrated in the families of Durr *et al*. (1995). They mention that 'slow-saccades were very early findings. Reduced saccadic velocity was associated with limited eye movements later in the disease and evolved gradually to complete gaze palsy in seven patients'. Similarly when members of the extended kindred of Gerstenbrand and Weingarden (1962) and their relatives who emigrated to Canada were examined by Lopes-Cendes *et al*. (1994) 30 years later, abnormal eye movements were observed in 81% of the affected individuals. Neuro-ophthalmological examination in four of them had revealed full pursuit eye movements with extremely slow saccades in the range of 100 to 300°/s. It appears that what Gerstenbrand and Weingarden (1962) described as conjugate paresis was indeed the later stages of slow saccades.

It is pertinent, here, to point out the possible neuroanatomical basis of the slow saccade, in order to distinguish it from other ophthalmoplegias. Autopsy examination of patients reported then by Wadia (1984, 1991, 1993*a*) and others (Mass and Scherer, 1933; Sigwald *et al*., 1963; Koeppen and Hans, 1976; Koeppen *et al*., 1977; Durr *et al*., 1995) have shown no degeneration of the third, fourth, or sixth cranial nerve nuclei. In fact, morphometry of the brainstem of two of Wadia's patients (Buttner-Ennever *et al*., 1985, 1986; Wadia, 1991, 1993*a*) demonstrated marked loss of large and medium sized neurons in a restricted area of the paramedian pontine reticular formation. More recently (Horn *et al*., 1996) parvalbumin immunoreactivity was used as a marker to examine the brainstem of one of them. It revealed, for the first time in humans, that the slowed horizontal saccade could be correlated with severe loss of premotor excitatory burst neurons in the paramedian pontine reticular formation, whereas the omnipause neurons were only slightly affected.

In an earlier publication of very similar, but genetically unmapped, Indian families, Kulkarni and Wadia (1975) demonstrated a severe reduction of the saccadic velocity, which ranged from 12.5 to 25% of the mean value in normal control subjects. The velocity measurement in the families now mapped to the SCA2 locus, reported here, confirm these observations. It is interesting that the clinical disability score of ocular movements reasonably matched the saccadic velocity measurements calculated later. Whilst the lowest saccadic velocity (67 ± 20°/s) was 22% of the normal average control value in the patient, with obvious slowing of the eyes, a remarkable head–eye lag and constant head thrust (score 3), it was only slightly but significantly reduced (263 ± 17.5°/s) in the patient in whom the slowing was just perceptible (score 1). Similarly, in Pedigree VI, the saccadic velocity was 100.2 ± 12.4°/s in the brother (III.5) after 15 years of the disease, with a disability score of 4, whilst in his older sister (III.4) whose disease was of later onset and shorter duration, the velocity was 162.01 ± 23.9°/s and the score 1. In their elder unaffected brother (III.2), the velocity was 322.5°/s (Table 3).

Though slow saccades and ophthalmoplegia have been reported in SCA1 and SCA3 patients (Dubourg *et al*., 1995; Giunti *et al*., 1995; Burk *et al*., 1996; Durr *et al*., 1996; Filla *et al*., 1996), the frequency compared with SCA2 patients varies in these publications. Yet, the overall impression is that it is clearly greater in SCA2 patients. This discrepancy is largely resolved by observations of Burk *et al*. (1996) who performed an analysis of 20° horizontal eye movements, by electro-oculography amongst patients with SCA1, SCA2 and SCA3. They found the saccadic velocity to be reduced in 100% of patients with SCA2, in 56% of patients with SCA1 and in 30% of patients with SCA3. More significantly, the velocity was severely reduced with SCA2 (137.9°/s), moderately reduced with SCA1 (244.4°/s) and only marginally reduced with SCA3 (347.7°/s). Normal control subjects had a saccadic velocity of 383.8°/s. In a later publication, Burk *et al*. (1997) saw slow saccades more frequently in SCA2 patients (81.5%). Electro-oculography of seven recorded a mean saccadic velocity of 120°/s, compared with 442.2°/s in healthy volunteers. Admittedly, at times it may be difficult in an individual patient to differentiate the SCA2 subtype early in the disease from SCA1, and evaluation of the associated signs may become necessary to arrive at the clinical diagnosis. But it must be stressed that, in the SCA2 subtype, the ocular slowing and even the head thrust appear, early at the onset, and progress concomitantly with the increasing ataxia, whilst in SCA1 the slowing is less remarkable compared with the ataxia, and can be missed in the absence of ocular symptoms. Here multidimensional oculographic measurement would be required to arrive at a specific diagnosis (Rivaud-Pechoux *et al*., 1998). From this and our own experience it can be deduced that slow saccades are more likely to be detected at the bedside in SCA2 than SCA1 or SCA3 patients. We believe that it would be rare to find a family of SCA2 in whom the slow saccades and the succeeding ophthalmoplegia are not found on clinical examination of the propositus and/or ataxic members of his/her family. The same cannot be said of SCA1 or SCA3 families.

In Table 5 we have included all reported pedigrees with cerebellar ataxia, slow saccades and ophthalmoplegia mapped to the SCA2 locus. From the previously reported, very similar, genetically unmapped families referred to earlier, those of Orozco Diaz *et al*. (1989, 1990), Gerstenbrand and Weingarten (1962) and Starkman *et al*. (1972), like ours (Wadia and Swami, 1971; Wadia, 1984, 1991, 1993*a*), have now all been mapped to the same SCA2 locus (Gispert *et al*., 1993; Pulst *et al*., 1993; Lopes-Cendes *et al*., 1994; Pang *et al*., 1997; Wadia *et al*., 1997; and this study). It will be interesting to see how many of the remaining families will show expansion at this same locus. We believe it will be the majority.

The electromyography and nerve conduction study of eight patients tested here is revealing. The sensory nerve action

potentials were markedly attenuated in all the nerves of the upper limbs, but only in two sural nerves, indicating that the sensory neuropathy affects the upper limbs earlier, and more, than the lower limbs. Further, it shows that the electrophysiological examination can be in advance of the clinical, in detecting the neuropathy, as the tendon reflexes (usually the sole manifestation of lower motor or sensory neuron disorder) were absent in only four of the eight patients and wasting of the hands in only one. Indeed, the sensory nerve action potentials were significantly attenuated in a patient with brisk reflexes.

An earlier electromyographic and sural nerve biopsy study of very similar but unmapped Indian families (Wadia *et al*., 1980; Wadia, 1984) had made such observations too. The sensory nerve action potentials were abnormal in 11 of their 12 patients, with conduction velocity in the normal range, when recordable. In two of these patients, the tendon reflexes were brisk and in one normal. Electromyography showed denervation in eight individuals with motor conduction velocity in the normal range. Two of them had preserved tendon reflexes. Sural nerve biopsy performed in five patients showed axonal degeneration, predominantly in the large myelinated fibres. The study concluded that the existence of clinically evident or subclinical axonal neuropathy is a consistent feature of this subtype of ADCA.

Similarly, abnormal tendon reflexes, often depressed or absent, and impaired vibration sense have also been reported as the next important sign in most genetically confirmed SCA2 families. A whole range of less common associated signs, of varying frequency amongst the different families, have been mentioned. These comprise mild spasticity, hyperreflexia and plantar extensor (Orozco Diaz *et al*., 1989, 1990; Sasaki *et al*., 1991; Durr *et al*., 1995, 1996; Burk *et al*., 1996, 1997; Filla *et al*., 1996; Geschwind *et al*., 1997); amyotrophy, and perioral and limb fasciculations (Lopes-Cendes *et al*., 1994; Durr *et al*., 1995; Giunti *et al*., 1995; Filla *et al*., 1996; Burk *et al*., 1996, 1997; Geschwind *et al*., 1997); mental deterioration (Orozco Diaz *et al*., 1989, 1990; Durr *et al*., 1995, 1996; Cancel *et al*., 1997; Geschwind *et al*., 1997); optic atrophy (Durr *et al*., 1995); dysphagia (Burk *et al*., 1996, 1997; Filla *et al*., 1996; Geschwind *et al*., 1997); and bladder dysfunction (Filla *et al*., 1996; Burk *et al*., 1997). These are, with exceptions, neither frequent nor dominant or present from the onset of the disease, although they do indicate a certain degree of interfamilial heterogeneity. There was considerable inter- and intrafamilial homogeneity amongst our kindreds, and in the presence of cerebellar ataxia and slow saccades in all, it was not difficult to identify this sub-type consistently, even before genotyping. After our initial publications, very similar genetically unmapped (R. S. Wadia *et al*., 1976; Sinha and Birendra Singh, 1989) and mapped (Sinha *et al*., 1998) Indian families have been reported, and similar families have been seen by colleagues all over India.

However, considerable phenotypic heterogeneity has been demonstrated by Geschwind *et al*. (1997), primarily in a number of ethnic groups. In these cases, genotype analysis has proved an essential adjunct for clinical diagnosis. The authors mention dementia as a very prominent and early feature in an African-American kindred and contrast it with a Machado–Joseph disease phenotype in a kindred of Swedish ancestry and with the 'typical' dominant ataxia with a mild course which would resemble our families. Difficulty in clinical diagnosis is understandable if dementia is considered in isolation. However, 92% of the patients in the series of Geschwind *et al*. (1997) exhibit slow saccades, 60% ophthalmoparesis and 44% peripheral neuropathy, facilitating a provisional diagnosis of SCA2, even before genetic investigation. Further, the general conclusion of Geschwind *et al*. (1997), that dementia is a prominent identifying sign of SCA2, is made on a somewhat dubious premise. Although they claim that severe dementia was present in 37% of the affected individuals studied, in reality these patients are confined to a single African-American pedigree. In our experience, and that of most others (Sasaki *et al*., 1991; Pulst *et al*., 1993; Belal *et al*., 1994; Ihara *et al*., 1994; Lopes-Cendes *et al*., 1994; Filla *et al*., 1995, 1996; Giunti *et al*., 1995; Burk *et al*., 1996, 1997), dementia is rarely observed. One possible exception to this has been reported in yet another small ethnic group of Martinique kindreds (Cancel *et al*., 1995; Durr *et al*., 1995, 1996), where severe dementia and cognitive impairment is frequent, even in the youngest patients. Once again, remarkable slow saccades, ophthalmoplegia and decreased tendon reflexes are universally present.

It now appears that the SCA2 phenotype, first recognized in India is seen world wide and in all races. It is likely that the phenotypic variability, when present, may be related to the ethnic origins of the respective populations studied. From our experience, and those of seasoned Indian neurologists, it appears that SCA2 is the most common ADCA amongst Indians.

In conclusion, we have shown here that six Indian families, including 12 asymptomatic members, segregating ADCA, slow saccades and peripheral neuropathy, show pathological expansion at the SCA2 locus. It is reasonable to assume that the same mutation will be present in the 25 phenotypically-similar pedigrees previously reported by N.W. We feel that 'ophthalmoplegia' as a generic term should be better defined in any clinical analysis of hereditary or degenerative ataxias. While other associated signs do lead to some degree of inter- and intra-familial heterogeneity, the core signs of cerebellar ataxia, slow saccades and depressed tendon reflexes are the hallmark of this entity as revealed by our families. However, phenotypic variability amongst diverse ethnic populations is conceivable, and may be related to different haplotypes. Our experience, and a review of the relevant world literature, shows that the 'fixed eyes' with limitation of the range of ocular movements described in this phenotype often result from progression of saccadic slowing. Examination of mildly affected family members offers an opportunity to confirm slowing of saccades clinically and a clue to the diagnosis.

Though slow saccades have been recorded in SCA1 and SCA3, they occur less consistently and more mildly than in SCA2, and the associated signs are different and at times distinguishing the phenotype.

We have found that a holistic approach to the diagnosis, taking into account the natural history, careful clinical assessment, pedigree analysis, electrophysiological tests and neuroimaging to identify the clinical phenotype, can often predict the genotype. It is believed that the genotyping will settle all the outstanding issues of classification and understanding of ADCAs, but phenotyping also has its own importance.

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