Autosomal dominant cerebellar ataxia type I
Clinical features and MRI in families with SCA1, SCA2 and SCA3


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Summary
Sixty-five patients suffering from autosomal dominant cerebellar ataxia-I (ADCA-I) were subjected to a genotype-phenotype correlation analysis using molecular genetic assignment to the spinocerebellar ataxia type 1, 2 or 3 (SCA1, -2 or -3) locus, clinical examination, eye movement recording and morphometric analysis of MRIs. Pyramidal tract signs, pale discs and dysphagia were more frequent in SCA1 compared with SCA2 and SCA3 patients. Saccade velocity was reduced in 56% of SCA1 and all SCA2, but only in 30% of SCA3 patients. MRIs of SCA2 patients showed atrophy changes typical of severe olivopontocerebellar atrophy (OPCA). The morphological changes in SCA1 were similar but less pronounced. In contrast, SCA3 patients had only mild cerebellar and brain stem atrophy distinct from typical OPCA. The principal finding of this study is that mutations of the SCA2 and SCA3 gene cause phenotypes which can be distinguished in vivo by recording of eye movements and morphometric MRI analysis. Correlative plotting of saccade velocity and diameter of the middle cerebellar peduncle yields a clear separation of SCA2 and SCA3. Spinocerebellar ataxia type I falls into an intermediate range that overlaps with both SCA2 and SCA3. However, the clinical syndrome observed in SCA1 patients is different from that in SCA2 and SCA3.

Keywords: autosomal dominant cerebellar ataxia; saccade velocity; trinucleotide repeat

Abbreviations: ADCA = autosomal dominant cerebellar ataxia; EOG = electrooculography; MJD = Machado-Joseph disease; OPCA = olivopontocerebellar atrophy; SCA1, -2 or -3 = spinocerebellar ataxia type 1, 2 or 3

Introduction
The ADCAs are a heterogeneous group of dominantly inherited disorders characterized by progressive ataxia that results from degeneration of the cerebellum and its afferent and efferent connections. Although manifestations of cerebellar disease are predominant in ADCA, there is often clinical and neuropathological evidence for involvement of brainstem, basal ganglia, spinal cord, retina or PNS. Degeneration of one or more of these anatomical structures may be present in most families (Greenfield, 1954; Harding, 1982).

Classifications of ADCA have been unsatisfactory as long as the underlying genetic defects were unknown. Traditionally, classifications were based on neuropathological criteria. Thus, Holmes (1907) distinguished between spinocerebellar degeneration, degeneration of the cerebellar cortex and OPCA. More recently, a clinical classification introduced by Harding gained wide acceptance. Harding separated ADCA into several types, the most common of which, ADCA-I, is characterized by supranuclear ophthalmoplegia, optic atrophy, basal ganglia symptoms, dementia and amyotrophy. Autosomal dominant cerebellar ataxia-II is distinct in having the additional feature of retinal degeneration, whereas ADCA-III is characterized by a pure cerebellar syndrome (Harding, 1982). Machado-Joseph disease (MJD) is a dominantly inherited ataxic disorder with large phenotypic variation. Machado-Joseph disease was first observed in patients of Azorean descent (Rosenberg et al., 1976; Coutinho and Andrade, 1978). Although MJD patients may have clinical features, such as prominent eyes, severe...
dystonia and amyotrophy, which are less frequently found in North American and European ADCA families, there is no clinical evidence to separate MJD from ADCA-I (Harding, 1982).

Genetic heterogeneity of ADCA-I has been established, with disease loci assigned to chromosome 6p (SCA1), 12q (SCA2), 14q (SCA3) and 16q (SCA4) (Zoghbi et al., 1991; Gispert et al., 1993; Gardner et al., 1994; Stevanin et al., 1994). Machado–Joseph disease families have been mapped to a locus on chromosome 14q, coincident with the localization of SCA3 (Takiyama et al., 1993). Two of the genes (SCA1, MJD) have been isolated, and the mutations have been shown to be unstable trinucleotide (CAG) repeat expansions present within coding regions of the respective genes (Orr et al., 1993; Kawaguchi et al., 1994). The MJD mutation occurs also in European and North American SCA3 families, confirming that the genetic basis of SCA3 and MJD is the same (Haberhausen et al., 1995; Matilla et al., 1995). In SCA1 and SCA3, there is an inverse correlation between the length of the CAG repeat and the age of onset, with the largest alleles occurring in patients with juvenile disease onset (Orr et al., 1993; Kawaguchi et al., 1994). In SCA3, patients with marked pyramidal and basal ganglia signs tend to have larger alleles than patients with less severe disease (Maciel et al., 1995).

The identification of various disease loci underlying ADCA-I raises the question whether the different mutations are associated with distinct clinical phenotypes. Initial studies failed to establish clinical differences between SCA1 and SCA3 (Dubourg et al., 1995). Studies describing the clinical features of SCA2 emphasized the high prevalence of saccade slowing and the absence of pyramidal tract involvement (Orozco et al., 1990; Lopes-Cendes et al., 1994; Dürr et al., 1995). Direct clinical comparisons of SCA2 with SCA1 or SCA3, however, have not been reported. In this study, we compared the clinical presentation of SCA1, SCA2 and SCA3 families. We used electrooculography (EOG) to measure saccade velocity and quantitative analysis of MRI to study brain morphology in vivo.

Patients and methods

Patients

Twenty-one families with a molecular diagnosis of SCA1, SCA2 or SCA3 were selected from the Tübingen ataxia database. At present, this database includes 48 ADCA families. All patients (n = 65) fulfilled diagnostic criteria of ADCA-I which were (i) progressive, otherwise unexplained ataxia in association with at least one of the following signs: saccade slowing, ophthalmoplegia, spasticity, extensor plantar responses, decreased vibration sense, or dystonia; and (ii) autosomal dominant inheritance. All patients were personally interviewed and examined clinically by one of us (K.B.) using a standardized examination procedure. Severity of cerebellar symptoms was rated on a scale ranging from zero (absent) to five (most severe) (Klockgether et al., 1990). Electrooculography and MRI were performed in 29 patients. For comparison, two groups of age- and sex-matched healthy volunteers were studied (EOG, n = 30, age, 47.2 ± 2.7 years; MRI, n = 36, age, 46.1 ± 2.4 years).

Molecular genetics

For the CAG amplification of the SCA1 region, each 0.025 ml reaction contained 60 nM of the SCA1-FP (5'-FAM-CAGCTGGAGGCTATTCACACTG-3') and SCA1-1952 (5'-TGTAGAGCCCGGAGGCTGTGAGG-3') primers (Orr et al., 1993). For the CAG repeat amplification of the SCA3/MJD gene, each 0.025 ml reaction contained 800 nM of the MJD-2-FP (5'-FAM-TTGATCGTGAAACAATGTATTT-3') and of the MJD25 (5'-TGGCCTTTTCATGGATGTGAA-3') primers (Kawaguchi et al., 1994). In addition, each reaction contained 0.08 mM dNTPs (SCA3/MJD: 0.16 mM), 1.5 mM MgCl2, polymerase buffer, 10% dimethylsulphoxide and 200 ng genomic DNA. After a first denaturation step at 94°C for 5 min, 1.5 U of TAQ polymerase was added to the reaction mix. The cycling conditions for 35 cycles were, as follows: denaturation at 94°C for 45 s, annealing at 65°C for 30 s (SCA3/MJD: 51°C), elongation at 72°C for 5 min followed by a terminal elongation step at 72°C for 5 min. The size of the polymerase chain reaction products was determined on an automatic analyser (Genescan, ABI, Foster City).

All subjects from the families without CAG expansion at the SCA1 or SCA3/MJD loci were genotyped for three microsatellite markers which span 2cM on chromosome 12q: cen-D12S105–lcM-D12S1339(1328)–lcM-D12S1340 (1329)-tel (Gispert et al., 1995; Krauter et al., 1995). Genotypes were determined by the polymerase chain reaction/blotting technique of Hazan et al. (1992), with slight modifications. TAQ polymerase (1.0 U) was added during the first denaturation step. Samples then underwent 35 cycles of denaturation at 94°C for 15 s, annealing at 55°C for 15 s and elongation at 72°C for 15 s followed by a terminal elongation step of 2 min. Pairwise lod scores were calculated using the MLINK program of the computer package LINKAGE (version 5.1) (Lathrop and Lalouel, 1991). Autosomal dominant transmission and a disease gene frequency of 10⁻⁴ were assumed. Five liability classes calculated according to Ott (1991) were used to take into account the age-dependent penetrance: 0–14 years, 0.075; 15–30 years, 0.3; 31–44 years, 0.574; 45–60 years, 0.803; 60 years, 0.955. Allele frequencies were computed from at least 27 unrelated caucasian controls. Equal recombination fractions were assumed for men and women.

Electrooculography

Eye movements were recorded by standard DC EOG methods with a quasi infinite time constant using silver–silver chloride electrodes. Data were written to strip charts. Saccade velocity
(° s⁻¹) was calculated by manually determining the maximal slope of the eye position signal of horizontal saccades. Average values of eight 20° centripetal and centrifugal saccades in both directions made to single light targets, are reported.

**MRI**

MRI was performed using a 1.5 T superconducting system (Magnetom, Siemens AG, Erlangen, Germany) with a circularly polarized head coil. Data were acquired and displayed on a 256×256 matrix. A standard examination program was used which consisted of the following measurements: sagittal and axial T₁-weighted spin echo images (TR, 600 ms; TE, 15 ms; NEX 1), axial proton density and T₂-weighted spin echo images (TR, 1800 ms, TE, 45/90 ms; NEX 1). All images had a slice thickness of 4 mm and were acquired without a gap by two subsequent, interleaved measurements. For quantitative evaluation an image analyser and a computerized interpretation program using software to overcome partial volume effects was used (Wüllner et al., 1993). For each case, the individual tissue signal intensity and the CSF signal intensity were defined at the fourth ventricle and the cerebellar hemispheres, respectively. These measurements gave two sets of normal distributed data. To determine exactly the amount of tissue within an interactively defined region of interest, all pixels with tissue signal intensity higher than the mean tissue value were summed. Those voxels with signal intensities between the mean tissues value and the mean CSF value were weighed according to their tissue content to take partial volume effects into account. Hereby, an effective number of tissue voxels within the region of interest was calculated. This technique permits measurement of the amount of tissue within a region of interest without the necessity to outline a border between tissue and CSF which is particularly difficult for the cerebellum. To compensate for individual variations of head size, we measured the total area of the posterior fossa on the midsagittal plane and related each area measurement to the respective posterior fossa area.

The following areas were measured: cerebellar vermis on the midsagittal plane; at the level of the aqueduct; cerebellar hemispheres on the first parasagittal plane lateral to the middle cerebellar peduncle; fourth ventricle on the midsagittal plane; pontine base with the medial lemniscus as dorsal border on the midsagittal plane; medulla oblongata at the level of the inferior olivary complex on a horizontal plane; and the cervical spinal cord on a horizontal plane at the level of the dens. The maximum diameter of the middle cerebellar peduncle was measured on a horizontal plane using a distance algorithm.

All quantitative measures are expressed as a percentage of the mean control group value. A morphological diagnosis of OPCA was made, if the following criteria were fulfilled: (i) size of the cerebellar vermis or hemispheres below the 2 SD range of the control group; (ii) size of at least two within the following three anatomical structures below the 2 SD range of the control group (pontine base, medial cerebellar peduncle, medulla oblongata) (Wüllner et al., 1993).

**Statistical analysis**

Statistical analysis was performed individual by individual. The relationship between age at onset, saccade velocity, morphometric measures and CAG repeat number was evaluated through linear regression analysis. Statistical analysis of the clinical data was performed using the Kruskal–Wallis test (cerebellar rating) and χ² test (frequency of associated symptoms). Statistical differences of saccade velocity and morphometric measures were calculated by ANOVA followed by a Tukey test.

**Results**

**Molecular genetic analysis**

An expansion of the CAG repeat at the SCA1 locus was detected in nine affected individuals of eight families. The expanded alleles ranged from 47 to 52 repeats, the normal alleles from 28 to 32. Expansion of the CAG repeat at the SCA3 locus was detected in 32 affected individuals of 10 families. The expanded alleles ranged from 63 to 80 repeats, the normal alleles from 12 to 36. Linkage analysis was performed in three families without expansion at the SCA1 or SCA3/MJD loci with three microsatellite markers closely linked to the SCA2 locus on chromosome 12q. Pairwise lod scores between the disease locus and chromosome 12 markers are shown in Table 1. Positive lod scores were obtained in all families at the loci with a maximal value exceeding +3.0 for the combined data. A maximal lod score of +3.25 at a recombination rate of 0.00 for marker D12S105 in family 2 established linkage to the SCA2 locus. The families shared the same haplotype for the linked markers. Since the expected frequency of this haplotype is <1.5%, this result strongly suggests the existence of a common founder for the three families. A founder effect would not be surprising in this case, since the families, although not known to be related, come from the same village in the state of Bavaria. Taken together, these data indicate that the three families are of the SCA2 type.

**Clinical findings**

Mean age of onset of the examined affected individuals was 34.0±4.3 years in SCA1 (n = 9), 37.8±2.6 years in SCA2 (n = 24), and 41.5±2.3 years in SCA3 (n = 32). Disease duration was 10.3±2.5 years in SCA1, 11.4±1.5 years in SCA2, and 10.5±1.3 years in SCA3 (Table 2). There were no significant differences between the groups. Age of onset was negatively correlated with repeat length in SCA1 and SCA3 (SCA1: r = −0.76, P < 0.05; SCA3: r = −0.92, P < 0.001).
Dystonia was a rare finding (P < 0.01). In contrast, decreased or absent ankle reflexes were more severe in SCA1 compared with SCA2 (P < 0.01 versus SCA2; P < 0.05 versus SCA3). In addition, it was almost normal in SCA3 (347.7° ± 19.7° s⁻¹), whereas there was no difference between SCA2 and controls. Statistical analysis showed significant differences between SCA2 and other groups (P < 0.05 versus SCA1, P < 0.001 versus controls and SCA3). Parkinsonism was not encountered in any of the SCA groups. Similarly, saccade velocity and CAG repeat length were not significantly correlated in SCA1 and SCA3.

MRI morphometry
Figure 1 shows representative examples of T₁-weighted MRIs of the posterior fossa and cervical spinal cord in SCA1, SCA2 and SCA3. Morphometric MRI analysis revealed significant atrophy of the cerebellar vermis, cerebellar hemispheres, pontine base, middle cerebellar peduncle, medulla oblongata, cervical spinal cord and enlargement of the fourth ventricle in all SCA groups compared with controls. The only exception was the cerebellar hemispheres in SCA3 which were not reduced in size (Fig. 2). In SCA2 and SCA3, Parkinsonism was not encountered in any of the patients (Table 2).

Table 1 Pairwise lod scores for markers on chromosome 12q in three families

<table>
<thead>
<tr>
<th>Families</th>
<th>0.00</th>
<th>0.05</th>
<th>0.10</th>
<th>0.20</th>
<th>0.30</th>
<th>0.40</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>0.26</td>
<td>0.36</td>
<td>0.59</td>
<td>0.71</td>
<td>0.69</td>
<td>0.51</td>
</tr>
<tr>
<td>2</td>
<td>3.25</td>
<td>3.18</td>
<td>2.90</td>
<td>2.54</td>
<td>1.80</td>
<td>1.07</td>
</tr>
<tr>
<td>3</td>
<td>1.55</td>
<td>1.52</td>
<td>1.37</td>
<td>1.18</td>
<td>0.79</td>
<td>0.43</td>
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<tr>
<td>Total</td>
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<td>5.06</td>
<td>4.86</td>
<td>4.43</td>
<td>3.28</td>
<td>2.01</td>
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</table>

<table>
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<tr>
<th>Families</th>
<th>0.00</th>
<th>0.05</th>
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<th>0.20</th>
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<tbody>
<tr>
<td>1</td>
<td>1.41</td>
<td>1.39</td>
<td>1.41</td>
<td>1.32</td>
<td>1.00</td>
<td>0.63</td>
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<tr>
<td>2</td>
<td>1.78</td>
<td>1.73</td>
<td>1.53</td>
<td>1.28</td>
<td>0.81</td>
<td>0.42</td>
</tr>
<tr>
<td>3</td>
<td>0.44</td>
<td>0.42</td>
<td>0.37</td>
<td>0.30</td>
<td>0.17</td>
<td>0.07</td>
</tr>
<tr>
<td>Total</td>
<td>3.58</td>
<td>3.54</td>
<td>3.31</td>
<td>2.90</td>
<td>1.98</td>
<td>1.12</td>
</tr>
</tbody>
</table>

We found no significant differences between the groups.

Table 2 Clinical characteristics of SCA1, SCA2 and SCA3 patients

<table>
<thead>
<tr>
<th>Associated signs (%)</th>
<th>SCA1</th>
<th>SCA2</th>
<th>SCA3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle reflexes decreased or absent</td>
<td>11</td>
<td>75**</td>
<td>63**</td>
</tr>
<tr>
<td>Ankle reflexes increased</td>
<td>89</td>
<td>17**</td>
<td>19**</td>
</tr>
<tr>
<td>Extensor plantar response</td>
<td>33</td>
<td>25</td>
<td>13</td>
</tr>
<tr>
<td>Spasticity</td>
<td>78</td>
<td>29*</td>
<td>22**</td>
</tr>
<tr>
<td>Amyotrophy</td>
<td>11</td>
<td>33</td>
<td>31</td>
</tr>
<tr>
<td>Fasciculation-like movements</td>
<td>22</td>
<td>42</td>
<td>38</td>
</tr>
<tr>
<td>Decreased vibration sense</td>
<td>78</td>
<td>92</td>
<td>69</td>
</tr>
<tr>
<td>Vertical gaze palsy</td>
<td>33</td>
<td>63</td>
<td>56</td>
</tr>
<tr>
<td>Pale discs</td>
<td>56</td>
<td>10**</td>
<td>17*</td>
</tr>
<tr>
<td>Prominent eyes</td>
<td>11</td>
<td>21</td>
<td>25</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>89</td>
<td>54*</td>
<td>34**</td>
</tr>
<tr>
<td>Bladder dysfunction</td>
<td>44</td>
<td>71</td>
<td>47</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0</td>
<td>4</td>
<td>13</td>
</tr>
</tbody>
</table>

Age and duration are given as means SE. *P < 0.05; **P < 0.01 versus SCA1.
Autosomal dominant cerebellar ataxia

Fig. 1 T1-weighted MRIs of infratentorial brain structures showing the posterior fossa in the midsagittal plane (upper left) and axial images at the level of the middle cerebellar peduncles (upper right), inferior olive complex (lower left) and dens axis (lower right). (A) MRI of a 43-year-old healthy male. The areas and distances that were measured are indicated by dashed lines. (B) MRI of a 44-year-old male SCA1 patient. (C) MRI of a 38-year-old female SCA2 patient. (D) MRI of a 41-year-old male SCA3 patient.

cerebellar hemispheres were smaller in SCA2 than in SCA3 ($P < 0.05$). There were no differences between SCA1 and SCA3 (Fig. 2). Using morphometric criteria (Wüllner et al., 1993), a diagnosis of OPCA was made in 33% of SCA1, 75% of SCA2 and in 8% of SCA3 patients. There was no significant correlation between size of the anatomical structures and disease duration in any of the SCA groups. Similarly, size of anatomical structures and CAG repeat length were not correlated in SCA1 and SCA3.

Discussion

In an attempt to identify characteristic phenotypic features of the mutations leading to ADCA-I, we compared patients with the SCA1, SCA2 and SCA3 mutation. Diagnosis of SCA1 and SCA3 ataxia was made by demonstration of CAG repeat expansion at the SCA1 and SCA3/MJD loci in eight and 10 families, respectively. In three families without expansion at these loci linkage analysis with markers closely linked to the SCA2 locus was performed. Although positive
Fig. 2 Size of cerebellar vermis (A), cerebellar hemispheres (B), middle cerebellar peduncles (C), pontine base (D), medulla oblongata (E) and cervical spinal cord (F) in SCA1, SCA2, SCA3 and controls, as determined by MRI morphometry. The size of each structure is expressed as the percentage of the respective control value. The individual data and the group means are shown. Significances: **P < 0.01, ***P < 0.001 versus controls; +P < 0.05, +++P < 0.001 versus SCA3; xxP < 0.01, xxxP < 0.001 versus SCA1.

lod scores were obtained in all families, linkage was established only in one family. However, the families came from the same village and shared the same haplotype, suggesting a common founder and a SCA2 genotype in these families.

The principal and novel finding of this study is that
mutations of the SCA2 and SCA3 gene cause phenotypes which can be distinguished in vivo by recording of eye movements and morphometric MRI analysis. Spinocerebellar ataxia type 2 is characterized by saccade slowing and MRI changes typical for OPCA with severe shrinkage of the middle cerebellar peduncles. In SCA3, saccade velocity is almost normal and infratentorial atrophy is mild and untypical for OPCA. Correlative plotting of saccade velocity and diameter of the middle cerebellar peduncle yields a clear separation of SCA2 and SCA3. Spinocerebellar ataxia type 1 falls into an intermediate range that overlaps with both SCA2 and SCA3 (Fig. 3). However, the clinical syndrome observed in SCA1 patients is different from that in SCA2 and SCA3 in that pyramidal tract signs, pale discs and dysphagia are more frequent.

The shared haplotype and the geographical origin of our SCA2 families suggest that they effectively represent one pedigree. It is therefore of critical importance to question whether this pedigree is representative for the SCA2 type of ADCA. Obviously, the present data do not allow a definite answer to this question. However, comparison of our families with SCA2 families previously reported show a high degree of resemblance (Orozco et al., 1990; Belal et al., 1994; Lopes-Cendes et al., 1994; Dürr et al., 1995; Filla et al., 1995). A final answer to this question will come from future studies including SCA2 families of different geographical and ethnical origin.

All patients suffered from a pan-cerebellar syndrome. Ataxia of upper limbs and action tremor were more severe in SCA2 patients than in SCA3 patients indicating major involvement of the cerebellar hemispheres in SCA2. Associated non-cerebellar symptoms may occur with all mutations. Pyramidal tract signs including hyperreflexia and spasticity were more frequent in SCA1 than in SCA2 and SCA3 patients (Schut, 1950; Zoghi et al., 1988; Goldfarb et al., 1989; Spadaro et al., 1992; Giunti et al., 1994; Dubourg et al., 1995; Genis et al., 1995; Kameya et al., 1995). However, pyramidal tract signs do not occur exclusively in SCA1. In the present study, there were similar findings in 20–30% of SCA2 and SCA3 patients. Earlier studies indicate that pyramidal tract signs are present in a higher proportion of SCA3 patients, in particular in those with an early disease onset (Takiyama et al., 1993; Dubourg et al., 1995; Matilla et al., 1995). Pale discs and dysphagia were frequent signs in SCA1, but did not occur exclusively in SCA1.

Slow saccades have been observed in several ADCA-I families (Wadia and Swami, 1971; Orozco et al., 1990). Because it is difficult to assess saccade velocity accurately by clinical examination, we used EOG. Although severe disability of some of the patients did not allow extensive studies of the saccadic system, recording of 20° horizontal saccades revealed highly significant differences between the mutations. Saccade velocity was severely reduced in SCA2 while it is usually normal in SCA3 and intermediate in SCA1. There is a clear distinction between SCA2 and SCA3 with little overlap of the individual data, whereas saccade velocity is extremely variable in SCA1 and falls into a range that overlaps with both SCA2 and SCA3. Saccade velocity has previously not been measured in ADCA patients with known genotype. However, slow saccades have been observed clinically in ~70% of the SCA2 cases of Cuban, Canadian, West Indian and Italian origin (Orozco et al., 1990; Belal et al., 1994; Lopes-Cendes et al., 1994; Dürr et al., 1995; Filla et al., 1995). In contrast, severe saccade slowing has been reported to be absent or is not mentioned in clinical descriptions of SCA3 (Takiyama et al., 1994; Dubourg et al., 1995; Maciel et al., 1995; Matilla et al., 1995).

The morphological changes of the cerebellum, brainstem and spinal cord, which underlie the various ataxic disorders can be studied quantitatively in vivo by MRI morphometry. These studies appear to be of particular importance because neuropathological abnormalities have been used for decades as the only criterion to distinguish between different forms of hereditary ataxia (Holmes, 1907; Greenfield, 1954; Klockgether et al., 1993). The present morphometric MRI data show an atrophy pattern suggestive of severe OPCA in the majority of SCA2 patients. As predicted by severe limb ataxia, there is often marked atrophy of the cerebellar hemispheres. The infratentorial abnormalities in SCA1 were similar but more variable and less pronounced. MRI changes suggestive of OPCA were present in 33% of the SCA1 patients. In SCA3, cerebellar and brainstem atrophy was mild and of a pattern incompatible with OPCA. The size of the cervical spinal cord was reduced in all three mutations. Although the number of post-mortem studies in cases with identified SCA1, SCA2 or SCA3 mutations is limited the results of these studies agree with the present quantitative MRI data. Post-mortem examinations of SCA1 cases showed OPCA of variable degree with involvement of ascending spinal pathways and minor degeneration of the pyramidal tract (Schut, 1950; Greenfield, 1954; Goldfarb et al., 1989; Spadaro et al., 1992; Genis et al., 1995; Kameya et al., 1995). Neuropathological examinations of Cuban SCA2 patients consistently revealed OPCA with marked reduction of Purkinje cells, degeneration of the inferior olives, pontine nuclei, and pontocerebellar fibres. The majority of Cuban
SCA2 patients had additional degeneration of posterior columns and spinocerebellar pathways, and cell loss in the substantia nigra (Orozco et al., 1989). Neuropathological findings in SCA3 are different from those in SCA1 and SCA2. The cerebellar cortex and the inferior olives are spared. The spinocerebellar tracts are most affected, along with degeneration of the vestibular and dentate nuclei. In most cases, the pontine base is only moderately affected. There is frequent involvement of the substantia nigra and the subthalamic pallidal connections (Rosenberg et al., 1976; Takiyama et al., 1994).

Our data show, not only phenotypical differences between the mutations, but also phenotypic variation within each mutation. The reasons for this variability are unknown. Correlation analysis failed to establish a relationship between saccade slowing or infratentorial atrophy and disease duration. Similarly, correlation of repeat length with saccade velocity and various morphometric variables in SCA1 and SCA3 did not yield significant results. In contrast, there was a high correlation between trinucleotide repeat length and age of onset, as reported in earlier studies (Orr et al., 1993; Kawaguchi et al., 1994). These data suggest that there are genetic or non-genetic factors other than trinucleotide repeat length and disease duration which influence phenotypic variation within each SCA mutation.

References


Received March 19, 1996. Revised May 16, 1996. Accepted June 13, 1996.