Clinical and Neuroradiological Features of Patients With Spinocerebellar Ataxias From Korean Kindreds

Oh Young Bang, MD; Kyooh Huh, MD; Phil Hyu Lee, MD; Hyon J. Kim, MD

Background: Comparative studies of clinical and magnetic resonance imaging findings in patients with spinocerebellar ataxias (SCAs) have been seldom reported.

Objective: To investigate clinical, genetic, and neuroradiological characteristics of SCAs in Korean kindreds.

Setting: University hospital.

Patients and Methods: Molecular analysis of SCA types 1, 2, 3, 6, and 7 and dentatorubral pallidoluysian atrophy and magnetic resonance imaging were performed in 67 patients with ataxia.

Results: The overall prevalence of 6 types of SCAs was 54% (36 of 67 patients), irrespective of patients' family histories. The most frequent type was SCA7 (11 patients, 16%), followed by SCA3 and SCA6 (10 patients, 15% for both). Certain clinical features suggested specific gene defects, although overlap among the 6 SCA subtypes was broad: visual disturbance was noted in patients with SCA3 and SCA6, dystonia in 1 patient with SCA6, and sporadic ataxia without pigmentary retinopathy in 1 patient with SCA7. Compared with the control subjects, patients with SCAs and multisystem atrophy had a significant enlargement of the fourth ventricle and atrophy of the cerebellum (P<.01). An inverse correlation between the pontine area and the degree of cerebellar atrophy was found in patients with multisystem atrophy (r = −0.73) but not in patients with SCAs. Magnetic resonance imaging revealed significant differences in pattern of morphological alterations among patients with different SCA gene mutations. A similar finding was observed in SCA patients with atypical phenotype.

Conclusion: The clinical and neuroradiological characteristics of Korean patients with SCAs might be helpful in detecting underlying gene mutations.

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utosomal dominant cerebellar ataxias (ADCAs) are a heterogeneous group of dominantly inherited disorders characterized by progressive ataxia. Advances in genetic analysis have made it possible to classify ADCAs into numerous types of spinocerebellar ataxias (SCAs) according to the specific mutations, and the increasing number of genes found to be associated with SCAs continues to broaden the differential diagnosis of SCAs.1-4

For decades, numerous efforts have been made to verify whether genetically defined subtypes of SCAs manifest distinct clinical phenotypes.5-8 Certain clinical features are more characteristic of some types of SCA, although overlap in clinical phenotypes has been observed in subjects with different genotypes.6,8-10 More recently, with the availability of magnetic resonance imaging (MRI), it has become possible to study the morphological structure of the brain in patients with SCAs. Distinct patterns of brain atrophy have been found in ADCA types I6,7 and III.11 However, comparisons of the clinical and MRI findings in patients with ADCA type II from Asian kindreds have seldom been reported.12

In this study, we investigated the molecular, clinical, and radiological features in patients with SCAs living in South Korea.

METHODS

From July 1, 2000, to July 30, 2002, consecutive patients manifesting progressive ataxia as a main clinical finding were included in this study. The patients were referred to the departments of neurology and medical genetics, spoke Korean, and had been living in South Korea for several generations. Sixty-seven individuals belonging to 52 unrelated kindreds were included. We received informed consent from all patients enrolled in the study. Age- and sex-matched control subjects (n = 20) with no evi-
idence of organic brain disease, such as migraine or tension headache, were selected to determine reference values for morphometric analysis.

Neurological examinations were performed by one of us (O.Y.B.), with specific attention to severity of illness and specific clinical features more characteristic of some types of SCAs (pyramidal and extrapyramidal symptoms, extraocular movement disorder, and bulbar symptoms) as follows: hyperreflexia for SCA1; muscle cramp, action tremor, and hyporeflexia for SCA2; fasciculation and dystonia for SCA3; pure cerebellar sign for SCA6; and visual disturbance for SCA7. Ophthalmologic evaluations were performed if patients complained of visual disturbance. The severity of ataxia (ataxia scale) was graded as follows: I, walking without assistance; II, walking with partial assistance; III, needing assistance walking; IV, needing assistance standing; and V, bedridden. Secondary forms of ataxia were excluded by the following tests when appropriate: MRI, cerebrospinal fluid analysis, tumor screening, history of alcohol abuse or toxin exposure, long-term treatment with antiepileptic drugs, vitamin B12, paraneoplastic antibodies (anti-Hu, anti-Yo, and anti-Ri), serum ceruloplasmin, and thyroid function. Genetic counseling was provided, with special attention to inheritance pattern and age at onset.

Fifty-two subjects with ataxia and 20 control subjects without neurological dysfunction were examined using 1.5-T MRI. T1-weighted axial and sagittal images, T2-weighted axial images, fluid-attenuated inversion-recovery, and diffusion-weighted images were obtained in transaxial and midsagittal planes (5-mm thickness). The anteroposterior and transverse diameters of the pons, midbrain, medulla oblongata, and fourth ventricle were measured on T1-weighted images and the putamen was measured on T2-weighted images by the methods previously published (Figure 1). The degree of atrophy in the cerebellar vermis and cerebellar hemisphere was assessed on the midsagittal plane and parasagittal plane, respectively, 5 mm lateral to the middle cerebellar peduncle. The degree of atrophy in the cerebellum and supratentorial structures was visually graded on a scale of 0 to 3 (0, none; 1, mild; 2, moderate; and 3, severe). The appearance of abnormal signal intensity of transverse pontine fibers was assessed on T2-weighted or fluid-attenuated inversion-recovery axial images. These measurements were performed independently by one of us (P.H.L.) and by another observer who was not informed of the clinical or genetic status of the subject. Magnetic resonance imaging–based volumetric analysis was also performed in 21 patients with ataxia by the method previously published. A neuroradiologist who was blinded to the clinical data manually measured the areas. Processing of all axial and sagittal T1-weighted magnetic data was performed using a commercially available computer workstation (Scion Image Beta 4.02; Scion Corp, Frederick, Md). The volumes of the pons and cerebellum were computed by multiplying the measured area per slice by the section thickness.

Genomic DNA of all patients was obtained by direct extraction of lymphocytes from fresh blood samples. For molecular genetic studies, previously published primer sequences and conditions for polymerase chain reaction were used to quantify the trinucleotide repeats associated with SCA1, SCA2, SCA3, SCA6, and SCA7 and dentatorubral pallidoluysian atrophy.

Figure 1. Measurements on T1- and T2-weighted magnetic resonance images. 1 Indicates the anteroposterior diameter of the putamen; 2, transverse diameter of the putamen; 3, anteroposterior diameter of the midbrain; 4, transverse diameter of the midbrain; 5, anteroposterior diameter of the pons; 6, transverse diameter of the pons; 7, width of the middle cerebellar peduncle; 8, anteroposterior diameter of the fourth ventricle; 9, transverse diameter of the fourth ventricle; 10, anteroposterior diameter of the medulla oblongata; and 11, transverse diameter of the medulla oblongata.
Table 1. Polymerase Chain Reaction Conditions for the Quantitation of CAG Repeats in Each Gene and the Range of Trinucleotide Repeats

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>Annealing Temperature, °C</th>
<th>Polymerase, Running Gel</th>
<th>Source of Primers Used</th>
<th>Name of Primer</th>
<th>Pathologic Allele (Normal Allele), Range of Repeats</th>
</tr>
</thead>
<tbody>
<tr>
<td>SCA1</td>
<td>55</td>
<td>2% Agarose, 6% polyacrylamide</td>
<td>Orr et al.17 1993</td>
<td>Rep1, Rep2</td>
<td>40-55 (25-37)</td>
</tr>
<tr>
<td>SCA2</td>
<td>63</td>
<td>2% Agarose, 6% polyacrylamide</td>
<td>Puls et al.16 1996</td>
<td>SCA2-A, SCA2-B</td>
<td>34-55 (16-22)</td>
</tr>
<tr>
<td>SCA3</td>
<td>61</td>
<td>2% Agarose, 6% polyacrylamide</td>
<td>Kawaguchi et al.14 1994</td>
<td>MJD52, MJD25</td>
<td>68-79 (13-36)</td>
</tr>
<tr>
<td>SCA6</td>
<td>68</td>
<td>2% Agarose, 6% polyacrylamide</td>
<td>Zhuchenko et al.13 1997</td>
<td>5-5-F1, 5-5-R2</td>
<td>22-28 (2-18)</td>
</tr>
<tr>
<td>SCA7</td>
<td>57</td>
<td>2% Agarose, 6% polyacrylamide</td>
<td>Johansson et al.15 1998</td>
<td>4U1024, 4U176</td>
<td>38-130 (7-17)</td>
</tr>
<tr>
<td>DRPLA</td>
<td>60</td>
<td>2% Agarose, 6% polyacrylamide</td>
<td>Ito et al.16 2002</td>
<td>DRPLA-F, DRPLA-R</td>
<td>49-75 (7-25)</td>
</tr>
<tr>
<td>MERRF</td>
<td>50</td>
<td>2% Agarose</td>
<td>Yoneda et al.17 1991</td>
<td>(8191-8210)F, (8345-8364)R</td>
<td>A8344G</td>
</tr>
</tbody>
</table>

Abbreviations: DRPLA, dentatorubral pallidoluysian atrophy; MERRF, mitochondrial encephalopathy with ragged red fiber; SCA, spinocerebellar ataxia.

Table 2. Age at Onset and Course of the Disease

<table>
<thead>
<tr>
<th>Course of Disease</th>
<th>SCA3 (n = 10)</th>
<th>SCA6 (n = 10)</th>
<th>SCA7 (n = 11)</th>
<th>Untyped (n = 10)</th>
<th>MSA (n = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset, mean ± SD, y</td>
<td>29 ± 10</td>
<td>35 ± 9</td>
<td>28 ± 10</td>
<td>26 ± 12</td>
<td>51 ± 7</td>
</tr>
<tr>
<td>Early (&lt;40)</td>
<td>9</td>
<td>7</td>
<td>9</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Later (&gt;40)</td>
<td>1</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>Ataxia scale, mean ± SD</td>
<td>2.2 ± 1.9</td>
<td>2.1 ± 1.8</td>
<td>2.1 ± 1.6</td>
<td>2.1 ± 1.8</td>
<td>2.3 ± 1.6</td>
</tr>
<tr>
<td>Prognosis</td>
<td>(n = 8)</td>
<td>(n = 8)</td>
<td>(n = 10)</td>
<td>(n = 8)</td>
<td>(n = 12)</td>
</tr>
<tr>
<td>Progression to walking aid, y</td>
<td>&lt;5</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>5-10</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>&gt;10</td>
<td>0</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ambulant without walking aid</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Abbreviations: MSA, multisystem atrophy; SCA, spinocerebellar ataxia.

(Table 1). For those who were not tested for expanded pathologic alleles and had a maternal inheritance pattern, we also screened for known mutations associated with mitochondrial encephalopathy with ragged red fiber (MERRF) as described previously.20 A clinical diagnosis of possible or probable multisystem atrophy (MSA) was made following the consensus statement guidelines published by Gilman and colleagues.21

All statistical comparisons in this study were done using χ2, 1-way analysis of variance, or Mann-Whitney tests. Correlation was calculated as Pearson's coefficient. Statistical significance was accepted at P < .05.

RESULTS

FREQUENCY OF EACH TYPE OF ATAXIA

The overall prevalence of 6 types of SCAs was 54% (36 of 67 patients), irrespective of family history. The most frequent type was SCA7 (11 patients, 16%), followed by SCA3 and SCA6 (10 patients, 15% for both). These 3 types together constituted 86% (31 patients) of the 36 patients with CAG expansions. Less frequent were SCA1 and SCA2, affecting 3% (2 patients) and 4% (3 patients), respectively. Point mutations in mitochondrial DNA were found in 3 patients. Among 28 patients who did not have expanded pathologic alleles, 18 (64%) were diagnosed clinically as having MSA and 10 (36%) were classified as having untyped ataxia. None of the expanded alleles were found in the dentatorubral pallidoluysian atrophy gene.

Of the 67 patients analyzed, 39 showed a dominant inheritance; the prevalence of 6 types of SCAs was 80% (31/39) in 23 families with a dominant inheritance (1 with the SCA1 gene, 2 with SCA2, 9 with SCA3, 9 with SCA6, and 10 with SCA7), 3 with the mutations associated with MERRF, and 5 patients did not have expanded pathologic alleles. Among the 28 patients without a family history of ataxia, 5 patients were genetically diagnosed as having SCAs (1 each with the SCA1, SCA2, SCA3, SCA6, and SCA7 gene).

Pedigrees of the patients with ataxia are available from one of us (H.J.K.).

AGE AT ONSET AND RATE OF PROGRESSION

The age at onset varied substantially in all subgroups (Table 2). The age at onset was significantly older in patients with MSA compared with the patients with SCAs (P < .001). The mean age at onset was older in patients with SCA6 compared with those with SCA3 and SCA7, but the difference was not statistically significant (P = .12). None of our patients with SCA6 had juvenile onset (before age 20 years), but 3 of 10 patients with SCA6 were afflicted after age 40. In patients with SCA7, the CAG repeat lengths correlated inversely with the age at onset (r = -0.95, P < .001), and the expansion of 1 CAG unit on average correlated with 2.2 years’ difference in age at onset. However, such findings were not observed in other types of SCAs (P > .05 for all).

In 49 transmissions of the patients with SCA3, SCA6, and SCA7, the age at onset of parents and offspring was obtained. The mean decrease in the age at onset in successive generations was 2.2 years’ difference in age at onset. However, such findings were not observed in other types of SCAs (P > .05 for all).
progressive generations was 12.2 years in SCA3, 11.8 years in SCA7, and 6.3 years in SCA6. However, it was not significantly different among the groups (P = .18). The repeat stability on transmission seemed to differ among the subtypes. A shortening of the CAG repeat number in successive generations was found in SCA7 (shortening of 15 and 7 CAG repeat numbers in 2 patients), which was not found in SCA3 (1 patient) and SCA6 (5 patients). Similarly, variability of the CAG repeat number among siblings was found in SCA7 (4 CAG repeats in 1 patient) and SCA3 (1-4 CAG repeats in 2 of 3 patients) but was not observed in the 6 patients with SCA6. The severity of ataxia did not differ among the subgroups.

Progression rate was defined as the time between the onset of symptoms and the requirement of a walking aid (Table 2). Among 32 patients with ataxia of more than 5 years’ duration, 28 patients (54%) were dependent on a walking aid. The time until need of a walking aid was shorter in the patients with MSA compared with those with SCAs (P = .001). There was a tendency among patients with SCA6 to have a more benign course of the disease, compared with those with SCA3 and SCA7, and all patients with SCA6 were still ambulant without a walking aid after 7 years with the disease. However, because of the small sample numbers, these differences were not significant (P = .12).

CLINICAL FEATURES OF THE PATIENTS WITH SCAs

Ataxia of gait and stance was present in all the patients with SCAs in this series. Cerebellar oculomotor signs differed significantly among the subtypes of SCA. Saccadic smooth pursuit and gaze-evoked nystagmus were frequently found in patients with SCA7 (7 of 10 patients, 70%) and SCA6 (all 10 patients), compared with other subgroups (none of 3 patients with SCA1, 1 of 2 patients with SCA2, and 5 of 11 patients with SCA7). In contrast, slow saccades were frequent in patients with SCA2 (all 3 patients, 100%) and SCA7 (7 of 11 patients, 64%), compared with patients with SCA1 (1 of 2 patients, 50%), SCA3 (4 patients, 40%), and SCA6 (1 patient, 10%). Visual disturbance was observed in all patients with SCA7 but was also found in 1 patient each with SCA3, SCA6, MERRF, and untyped ataxia. However, pigmentary retinopathy was exclusively found in patients with SCA7 and was observed in 10 of 11 of these patients. Action or postural tremor was observed in patients with SCA2 (all 3 patients, 100%), and untyped ataxia (1 of 10 patients, 10%). Otherwise, extrapyramidal signs did not differ between subgroups, although 1 patient with SCA6 with mild ataxia symptoms and signs showed disabling dystonia on the neck. Signs of pyramidal affection, including spasticity and hyperreflexia, were not found in patients with SCA2 and SCA6, were found frequently in patients with SCA1 (both patients, 100%) and SCA7 (8 of 11 patients, 73%), and were found rarely in patients with SCA3 (4 of 10 patients, 40%). Peripheral neuropathy was clinically obvious in all patients with SCA2 and in 4 patients with SCA3, but none of the patients with SCA1, SCA6, and SCA7 showed signs of peripheral involvement.

There were 7 patients with atypical phenotypic presentation. These included 1 each with sporadic SCA1 and SCA2, a patient with sporadic SCA3 with pure cerebellar syndrome, 3 patients with SCA6 (1 sporadic and 2 familial with dystonia or visual disturbance), and a patient with sporadic SCA7 without pigmented retinopathy. The phenotype in patients with untyped ataxia was highly variable. Most patients presented with a combination of ataxia, spasticity, dystonia, and action tremor, as frequently observed in SCA1, SCA2, SCA3, and SCA6. In patients with untyped disease, ataxia was accompanied by various other symptoms, and most patients had mild cerebellar symptoms and signs along with disabling symptoms. Two families had subjects with pronounced dystonia associated with several years’ duration of ataxia, and various degrees of spasticity were observed in another family. One patient with untyped ataxia had autonomic dysfunction (urinary problem and orthostatic hypotension), voice change (stridor), sleep apnea, and gait ataxia, which were also observed in his mother.

Magnetic resonance imaging was performed in 36 patients with SCAs (1 with SCA1, 2 with SCA2, 9 with SCA3, 6 with SCA6, 11 with SCA7, and 7 with untyped ataxia), 2 patients with MERRF, 14 patients with MSA, and 20 control subjects. The patients with ataxia (SCA and MSA groups) had a significant enlargement of the fourth ventricle and atrophy of the cerebellar vermis and hemispheres compared with the controls (P < .01 for both groups). However, brainstem atrophy was not consistently found among the patients with ataxia (Figure 2). Significant differences were observed between the patients with SCA7 and the control subjects in the anteroposterior and transverse diameters of the pons, the anteroposterior diameter of the medulla, and the diameter of the middle cerebellar peduncle (P < .01) but were not found in other types of SCA. The anteroposterior and transverse diameters of the pons, the anteroposterior diameter of the medulla oblongata, and the diameter of the middle cerebellar peduncle were significantly different between the patients with SCA7 and those with other types of SCA. The patients with MSA also had pontine atrophy (P < .05 for the anteroposterior and P < .01 for the transverse diameters of the pons), but the degree of pontine atrophy was more prominent in patients with SCA7 than in those with MSA (P < .05). Neither the anteroposterior and transverse diameters of the midbrain and globus pallidus nor the transverse diameter of the medulla oblongata differed significantly among the ataxia groups and control subjects. T2-weighted axial MRI revealed a high signal intensity in the transverse pontine fibers in nearly all the patients with MSA and in some patients with SCAs (1 each with SCA2 and untyped ataxia and 2 with SCA7), which was not observed in the patients with SCA3 or SCA6 (Figure 3). An acceptable level of interrater reliability was found for these measurements (κ > 0.68).

Figure 4 shows the patterns of cerebellar and pontine atrophy in each type of ataxia. An inverse correlation between the pontine area and the degree of cerebel-
lar atrophy (linear regression analysis) was found in patients with MSA ($r = -0.73, P = .007$) (Figure 4A) but not in patients with SCAs (SCA3, $r = -0.32, P = .41$; SCA6, $r = -0.01, P = .98$; and SCA7, $r = -0.32, P = .34$) (Figure 4B). Magnetic resonance imaging abnormalities in patients with SCA6 were somewhat homogeneous and demonstrated pure cerebellar atrophy, whereas pontine atrophy with any degree of cerebellar atrophy was a consistent finding among patients with SCA7 (Figure 4B).

Magnetic resonance imaging patterns in the patients with atypical clinical features were similar to those among patients with typical phenotypic presentation. These included mild cerebellar atrophy in a patient with sporadic SCA3 with pure cerebellar syndrome, marked
In this study, we investigated characteristic clinical and MRI features of patients with genetically confirmed SCA1, SCA2, SCA3, SCA6, and SCA7. In addition to a wide phenotypic overlap among the SCAs, significant interfamilial and intrafamilial phenotypic variabilities, even for each SCA subtype, have been described. These differences have been reported to be due to a variation in the number of CAG repeats among affected members of the same family. Because of the widespread availability of gene testing, increasing numbers of genes are being found to be associated with SCAs. Therefore, a recognition of characteristic features and MRI findings of some SCAs may be useful in the differential diagnosis. Synopses of characteristics may facilitate genetic screening by en-

**Figure 4.** Degrees of cerebellar and pontine atrophy in patients with each type of ataxia. The degree of cerebellar atrophy is the mean value of the degree of atrophy of the cerebellar vermis and hemisphere. The pontine area is obtained by multiplying the anteroposterior diameter by the transverse diameter of the pons. Asterisk indicates the inverse correlation of the pontine volume on volumetric analysis and the pontine area on manual measurement; and dagger, inverse correlation of the pontine volume on volumetric analysis and the pontine area on manual measurement; and asterisk, linear correlation of the pontine volume on volumetric analysis and the pontine area on manual measurement; and dagger, inverse correlation of the pontine area and cerebellar atrophy; M, multisystem atrophy; numbers in squares, spinocerebellar ataxia (SCA) type; U in circle, untyped ataxia; black squares signify SCA7s; gray, SCA6s; and open, SCA3s.

Cerebellar atrophy without pontine atrophy in 3 patients with SCA6 with atypical phenotypes (1 sporadic and 2 familial with dystonia or visual disturbance), and prominent pontine atrophy in a patient with sporadic SCA7 without pigmentary retinopathy (Figure 4B). Although most patients with untyped ataxia showed clinical phenotypes of ADCA I, their MRI findings were varied, ranging from normal to global atrophy of brain structures in the posterior fossa (Figure 4C).

Finally, we performed volumetric analysis in 21 patients with ataxia (7 with SCA3, 5 with SCA7, 1 with SCA6, 3 with untyped ataxia, 2 with MERRF, and 3 with MSA) to make certain that our measurements of pontine area and grading of cerebellar atrophy correlated with the results of volumetric analysis. We found a good correlation between our measurements and volumetric analysis, a linear correlation between pontine volume and ponti-

**Figure 5.** Correlation of pontine area and cerebellar atrophy with volumes of the pons (A) and cerebellum (B) measured by volumetric analysis. The volume of both structures is expressed as the percentage of the respective total intracranial volume. M indicates multisystem atrophy; MERRF, mitochondrial encephalopathy with ragged red fiber; numbers in squares, spinocerebellar ataxia (SCA) type; U in circle, untyped ataxia; asterisk, linear correlation of the pontine volume on volumetric analysis and the pontine area on manual measurement; and dagger, inverse correlation of the cerebellar volume on volumetric analysis and the degree of cerebellar atrophy on visual inspection. Black squares signify SCA7s; gray, SCA6s; and open, SCA3s.

tine area ($r = 0.85$, $P < .001$), and an inverse correlation between cerebellar volume and cerebellar atrophy ($r = -0.66$, $P = .001$) (Figure 5).

**COMMENT**
The intronic GAA repeat expansion of the Friedreich ataxia gene.28 The criteria for MSA. We analyzed 2 of these 5 patients for patients with sporadic ataxias did not meet the clinical criteria among those with no definite visual disturbance. However, Jin et al.26 reported that SCA2 was the most frequent hereditary ataxia and that there were no instances of SCA types 1 and 7 among Korean patients. However, their study included only 24 patients with SCAs, while our study enrolled a larger cohort. We found SCA7 to be a frequent cause in patients with MSA compared with those with SCAs, and all patients with MSA had onset after age 40. Age at onset was negatively affected by CAG repeat lengths in SCA7, but such a finding was not observed in the other types of SCA, probably because of small sample sizes. CAG repeat length was reported to be responsible for approximately 70% of the variability in the age at onset in SCA1, SCA2, SCA3, and SCA6.8 Similarly, in this study, the progression rate was higher in patients with MSA compared with those with SCAs; however, it was not different among the subtypes of SCAs.

Our data are in agreement with a widely accepted clinical classification introduced by Harding,7 who classified ADCA into several types. Type I ADCA is characterized by ophthalmoplegia, optic atrophy, basal ganglia symptoms, dementia, and amyotrophy. Type II is distinct in having the additional feature of retinal degeneration. Type III is characterized by a pure cerebellar syndrome. Ten (67%) of 15 patients with SCA1, SCA2, and SCA3 in this study were clinically diagnosed as having ADCA I, whereas 7 (70%) of 10 patients with SCA6 were diagnosed as having ADCA III, and 10 (91%) of 11 patients with SCA7 had ADCA II (Table 3). In our present study, ADCA classification had a sensitivity of 74.3% (the clinical ADCA classification matched the disease loci underlying ADCA in 26 of 35 patients with SCAs) and a specificity of 82.1% (among the 28 patients diagnosed as having non-ADCA, only 5 patients had a specific gene defect causing ADCA) to detect possible gene defects to be evaluated.

Several clinical features with some predictive value for specific gene defects have been reported, and the phe

<table>
<thead>
<tr>
<th>Table 3. Summary of Phenotypic Presentation of the SCAs and MSA</th>
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<tbody>
<tr>
<td><strong>Presentation</strong></td>
</tr>
<tr>
<td>Inheritance</td>
</tr>
<tr>
<td>SCA3</td>
</tr>
<tr>
<td>n = 10</td>
</tr>
<tr>
<td>Inheritance</td>
</tr>
<tr>
<td>ADCA I</td>
</tr>
<tr>
<td>ADCA II</td>
</tr>
<tr>
<td>ADCA III</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Specific features</td>
</tr>
<tr>
<td>Cramp, tremor, or hyporeflexia</td>
</tr>
<tr>
<td>Fasciculation or dystonia</td>
</tr>
<tr>
<td>Pure cerebellar sign</td>
</tr>
<tr>
<td>Visual disturbance (pigmentary retinopathy)</td>
</tr>
<tr>
<td>Autonomic dysfunction</td>
</tr>
</tbody>
</table>

Abbreviations: ADCA, autosomal dominant cerebellar ataxia; MSA, multisystem atrophy; NA, not applicable; SCA, spinocerebellar ataxia.

* Clinically ADCA type I, except family history.
† Clinically ADCA type II, except family history.
‡ Clinically ADCA type III, except family history.
§ Clinically ADCA type II, except family history.
notypes of SCAs in the present study confirmed the findings of other studies.\textsuperscript{6,8,13,15} The combination of slow saccadic eye movements, areflexia, muscle cramping, and action tremor was found in all our patients with SCA2, which was similar to the findings of Burk et al.\textsuperscript{8} Facio-lingual fasciculation, bulging eye due to lid retraction, and dystonia are reported to be characteristic symptoms of SCA3,\textsuperscript{13} and they were observed in half of the patients with SCA3 in this study. However, our data are also in agreement with those of Schols and colleagues,\textsuperscript{8} who found that phenotypic overlap between SCA types was broad. The typical clinical feature of SCA6 is a slowly progressive ataxia or an episodic ataxia and vertigo with downbeat nystagmus that evolves into a persistent ataxia.\textsuperscript{14} Dystonia has rarely been reported in SCA6\textsuperscript{30}; however, dystonia was the most striking clinical finding in 1 patient with SCA6 in our study. The SCA7 subtype is characterized by cerebellar ataxia and visual loss, and all our patients with SCA7 had such symptoms. However, visual disturbance was not unique to SCA7 and was observed in 4 patients with other types of ataxia (SCA3, SCA6, untyped ataxia, and MERRF) in this study, which is consistent with other previous reports.\textsuperscript{31-33} Although retinal degeneration in SCA3 has recently been reported,\textsuperscript{32} retinal degeneration on funduscopic evaluation was found exclusively in patients with SCA7 in our study. Autonomic failure causing urinary incontinence or orthostatic hypotension is a characteristic clinical feature of MSA. In our cohort, orthostatic hypotension and urinary incontinence were found in 1 patient with hereditary ataxia in whom no expanded pathologic allele was found. Despite similar symptoms found in his mother, we could not exclude the possibility of MSA because of the clinical (additional features such as stridor and sleep apnea) and MRI (olivopontocerebellar atrophy and high signal intensity in the transverse pontine fiber on T2-weighted axial image) findings that are characteristic of MSA.

Magnetic resonance imaging revealed significant differences in the pattern and extent of morphological alterations among patients with different SCA gene mutations. Characteristic MRI findings of ADCA I (SCA1, SCA2, and SCA3)\textsuperscript{2,10} and ADCA III (SCA6)\textsuperscript{11} have been previously reported. However, MRI findings among patients with ADCA II have been seldom reported,\textsuperscript{34} and there has been no comparative study of the MRI findings among the ADCA subtypes, to our knowledge. Our results showed that the correlation between pontine and cerebellar atrophy, which was observed in patients with MSA, was not found in patients with SCAs and that MRI abnormalities in patients with ADCA III (SCA6) and ADCA II (SCA7) were somewhat homogeneous, representing selective cerebellar and brainstem atrophy, respectively. A similar finding was observed in patients with SCAs with atypical phenotypes (sporadic or ataxia with atypical clinical presentation). Therefore, MRI results may enable physicians to conjecture the underlying mutations and to direct gene testing for these mutations. Pontine atrophy has been reported in other types of SCA, including SCA6\textsuperscript{33,34}; however, it is exceptional for such patients to have pontine atrophy with their cerebellum spared, which was observed in our patients with SCA7.

Severe cerebellar atrophy without pontine atrophy was observed in all patients with SCA6, which is consistent with findings of a recent postmortem study.\textsuperscript{37} The MRIs of patients with SCA3 disclosed only mildly atrophied pons and cerebellum, which is consistent with a previous report.\textsuperscript{6} Although atrophy of the midbrain and basal ganglia has been previously reported,\textsuperscript{7,11} we found no significant difference in the anteroposterior and transverse diameters of the midbrain and putamen between the patients with SCA3 and the control subjects. Magnetic resonance imaging findings of the patients with untyped ataxia were variable, as were their clinical phenotypes.

In this study, volumetric analysis was not performed in all the patients. Although an acceptable level of interrater reliability in the measurements was observed in the present study (κ=0.68), there might be some discrepancies between the volumetric analysis and our measurements. However, when we performed volumetric analysis in some patients by the method previously published,\textsuperscript{7} a good correlation between our measurements and volumetric analysis was found in pontine area and cerebellar atrophy. Nevertheless, further studies with more volumetric analysis are needed.

In conclusion, our results demonstrate that the clinical and neuroradiological characteristics of Korean patients with SCAs are similar to those of other populations, confirming previous observations among patients with SCAs in Korea.\textsuperscript{6,69} Finally, our data also suggest that MRI may play a role in detecting underlying gene mutations in patients with atypical phenotypic presentations.

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