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Extracerebellar Signs and Symptoms in 117 Korean Patients with Early-Stage Spinocerebellar Ataxia

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Background and Purpose Spinocerebellar ataxias (SCAs) are the most common form of hereditary ataxias. Extracerebellar signs have been well described and are helpful in differentiating the SCA subtypes. However, there are few reports on the early-stage extracerebellar signs in various SCA subtypes. This study explored the clinical and magnetic resonance imaging (MRI) characteristics of early-stage SCAs in the Korean population.

Methods We retrospectively reviewed the medical records of genetically confirmed SCA patients with a disease duration of <5 years. Data on baseline characteristics, extracerebellar signs, and initial MRI findings were organized based on SCA subtypes.

Results This study included 117 SCA patients with a median age at onset of 40.6 years. The family history was positive in 71.8% of the patients, and the median disease duration and the score on the Scale for the Assessment and Rating of Ataxia at the initial visit were 2.6 years and 5.0, respectively. SCA3 was the most prevalent subtype, and oculomotor abnormalities were the most frequent extracerebellar signs in early-stage SCAs. Saccadic slowing was characteristic of SCA2 and SCA7, and gaze-evoked nystagmus was prominent in SCA6. Parkinsonism was relatively frequent in SCA8 and SCA3. Decreased visual acuity was specific for SCA7. Dementia was not an early manifestation of SCAs. Brain MRI revealed a pattern of pontocerebellar atrophy in SCA2 and SCA7, while SCA6 demonstrated only cerebellar cortical atrophy.

Conclusions SCA patients exhibited diverse extracerebellar signs even in the early stage. Specific extracerebellar signs were characteristic of specific subtypes, which could facilitate differential diagnoses of early-stage SCAs.

Key Words spinocerebellar ataxias, extracerebellar signs, early stage, Korea.

INTRODUCTION

Cerebellar ataxia is classified into an acquired, hereditary, and degenerative ataxias, which result in limb incoordination, postural instability, and dysarthria.[1] Spinocerebellar ataxias (SCAs) are the most common form of hereditary ataxias,[2] and 48 genetically and clinically heterogeneous SCA subtypes have been identified.[3] Although cerebellar ataxia is the most characteristic sign in SCAs, patients often also exhibit extracerebellar signs and symptoms such as oculomotor abnormalities, extrapyramidal or pyramidal signs, decreased visual acuity, peripheral neuropathy, dysautonomia, and cognitive decline.[2]

Subtype-specific extracerebellar signs and symptoms have been well described in SCAs, but relatively little comparative research into early-stage extracerebellar findings according to subtype has been performed. An understanding of early-stage extracerebellar signs in SCAs would help to narrow the diagnosis by revealing genotype–phenotype correlations and enable a deeper understanding of the underlying disease mechanisms.

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This study investigated the clinical and magnetic resonance imaging (MRI) characteristics of early-stage SCAs in patients with a disease duration of <5 years. The aim was to facilitate the characterization of the race-specific extracerebellar signs in early-stage SCAs and early diagnosis.

METHODS

Patients

This study was approved by the Institutional Review Board of the Samsung Medical Center, Seoul, Korea, which waived the requirement to obtain informed consent (No. 2019-03-016). Initially, 157 patients with genetically confirmed SCAs were screened at the Movement Disorders Clinic of the Samsung Medical Center from January 2012 to March 2018. Patients with a disease duration of <5 years were subsequently selected, and those with insufficient clinical information (*n*=13) or without brain MRI findings (*n*=27) were excluded.

Data acquisition

We retrospectively reviewed medical records using a structured case-report form. The following patient information was collected: sex, age at onset, disease duration at the initial visit, presence of family history, number of trinucleotide repeats, initial score on the Scale for the Assessment and Rating of Ataxia (SARA),[4] and the disease stage (stage 0, no gait difficulties; stage 1, gait difficulties; stage 2, assisted gait, requiring a walking aid or reliance on a supporting arm; and stage 3, wheelchair-bound).[5] Age at onset was defined as the age at the first appearance of gait disturbance, dysarthria, or hand clumsiness. Slowness of movement, postural instability, involuntary muscle contraction, decreased visual acuity, and cognitive decline were also regarded as initial symptoms depending on the SCA subtype.[6] Family history was based on pedigrees, by which second-degree relatives with ataxia or unexplained gait disturbance were identified.

We determined the clinical manifestations that accompanied ataxia, such as oculomotor abnormalities, extrapyramidal or pyramidal signs, decreased visual acuity, hyporeflexia, dysautonomia, dementia, and bulging eyes. Extrapyramidal signs were considered to be present if patients exhibited parkinsonism, defined as bradykinesia and either rigidity or resting tremor,[7] dystonia, myoclonus, or chorea. Dysautonomia was considered to be present if urinary incontinence or retention, recurrent orthostatic dizziness or hypotension, or (for males) erectile dysfunction was reported.[6] The cognitive function of all patients was assessed using the Korean Mini-Mental State Examination (MMSE).[8] Dementia was diagnosed if the MMSE score was below 24 and the cognitive decline was sufficiently severe to impair the ability of the patient to perform the activities of daily living.[9] Some patients had undergone electrophysiological tests, and these results were analyzed when available.

Only the initial brain MRI findings were assessed, all of which were obtained using a 3.0-T system. The presence of atrophy or signal changes in the cerebellar hemispheres, vermis, pons, or middle cerebellar peduncles (MCPs) were assessed using T2-weighted axial images (repetition time of 3,000−6,960 ms, echo time of 80−130 ms, and thickness of 3.0−5.0 mm). Two movement-disorder specialists (M.K. and J.W.C.) who were blinded to the clinical information of patients evaluated the MRI findings separately. When discrepancies occurred, the final result was determined by consensus after referring to the sagittal images.

Genetic analysis was performed at a validated research laboratory at the Samsung Medical Center, Seoul, Korea using commercially available genetic panels that included SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, and SCA17.

Statistical analyses

The Kruskal-Wallis test was used to compare baseline characteristics between patients with different SCA subtypes. The data of one SCA17 patient were omitted from this statistical analysis to facilitate data interpretation. Fisher's exact test was used to investigate the frequencies of a positive family history, clinical symptoms, and MRI abnormalities according to SCA subtype. A p value of <0.05 was considered statistically significant. The interrater reliability of the MRI findings was assessed using the intraclass correlation coefficient (ICC). Statistical analyses were performed using commercially available software (SPSS Statistics, version 22, IBM Corp., Armonk, NY, USA).

RESULTS

Baseline characteristics

This study included 117 SCA patients (Table 1), with SCA3 being the most common (n=38, 32.5%), followed by SCA2 (*n*=31, 26.5%), SCA6 (*n*=19, 16.2%), SCA1 (*n*=13, 11.1%), SCA8 (*n*=8, 6.8%), SCA7 (*n*=7, 6.0%), and SCA17 (*n*=1, 0.9%). There was a family history for SCA in 71.8% of the patients. The median disease duration, SARA score, and disease stage at the initial visit were 2.6 years, 5.0, and 1.0, respectively.

Clinical manifestations

Gait disturbance was the most common initial complaint (Supplementary Fig. 1 in the online-only Data Supplement), and the included SCA patients exhibited various clinical manifestations in the early stage (Fig. 1, Supplementary Table 1 in the online-only Data Supplement). All patients experienced

Table 1. Baseline characteristics of SCA patients with a disease duration of <5 years

	SCA1	SCA2	SCA3	SCA6	SCA7	SCA8	SCA17	Overall	*p**
Number of patients	13 (11.1)	31 (26.5)	38 (32.5)	19 (16.2)	7 (6.0)	8 (6.8)	1 (0.9)	117 (100)	
Sex, male:female	5:8	19:12	19:19	12:7	3:4	5:3	0:1	63:54	0.626†
Family history	10 (76.9)	27 (87.1)	27 (71.1)	12 (63.2)	3 (42.9)	5 (62.5)	0 (0.0)	84 (71.8)	0.088†
TNR	44.0 [7.0]	41.0 [4.0]	69.0 [9.3]	23.0 [1.0]	44.0 [22.0]	96.0 [26.0]	42.0	44.0 [30.5]	0.000‡
Age at onset, years	44.7 [15.4]	37.5 [14.5]	39.3 [15.5]	41.6 [15.7]	19.6 [45.3]	44.1 [19.0]	43.5	40.6 [16.6]	0.200‡
Age at initial visit, years	48.3 [14.9]	40.1 [16.5]	43.2 [15.1]	44.8 [17.4]	24.0 [45.8]	48.0 [17.4]	43.5	43.2 [13.2]	0.186‡
Disease duration at initial visit, years	2.1 [3.9]	2.5 [4.3]	2.7 [4.5]	2.9 [3.0]	2.6 [2.5]	2.1 [2.5]	2.9	2.6 [3.3]	0.982‡
SARA score at initial visit	10.0 [5.5]	8.0 [3.0]	6.5 [8.3]	6.0 [4.0]	8.0 [3.0]	6.0 [8.3]	18.0	5.0 [5.0]	0.125‡
Disease stage	1.0 [0.0]	1.0 [1.0]	1.0 [0.0]	1.0 [0.0]	1.0 [0.0]	1.0 [0.0]	2.0	1.0 [0.0]	0.049‡

Data are *n* (%) or median [interquartile range] values.
*Data of one SCA17 patient were omitted, †Fisher's exact test, ‡Kruskal-Wallis test.
SARA: Scale for the Assessment and Rating of Ataxia, SCA: spinocerebellar ataxia, TNR: trinucleotide repeat number.

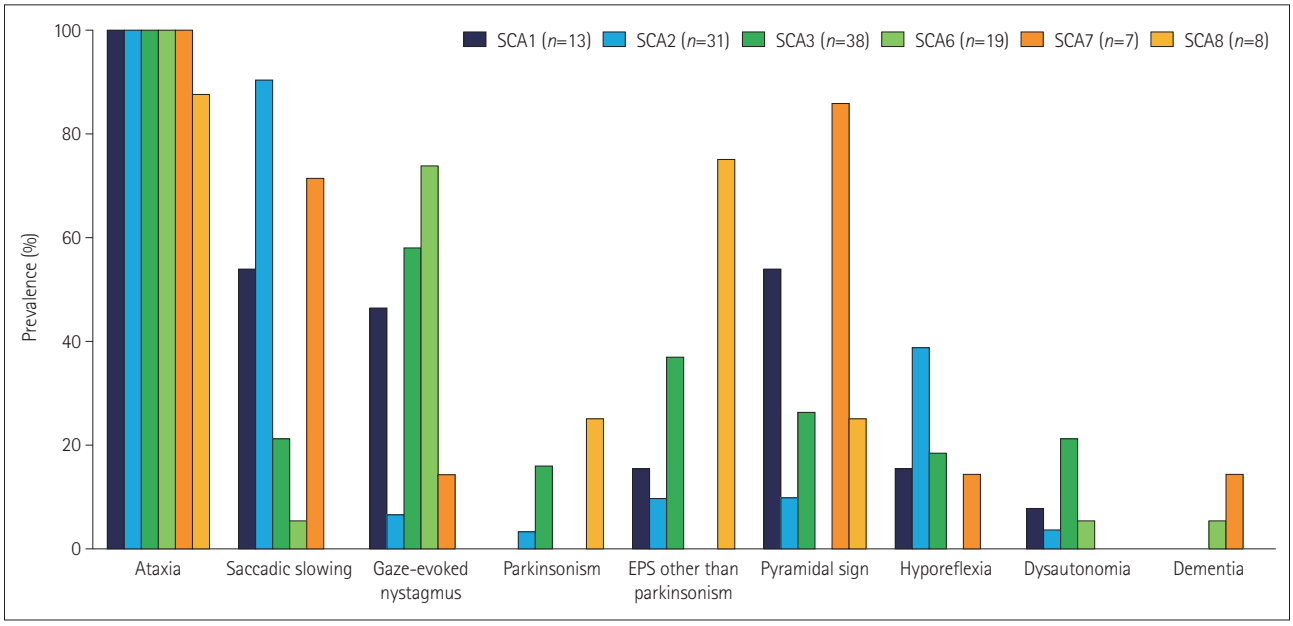

Fig. 1. Clinical characteristics at a disease duration of <5 years in SCA patients. SCA patients exhibited various clinical manifestations, some of which were characteristic of specific SCA subtypes. Data of one SCA17 patient were omitted. EPS: extrapyramidal signs, SCA: spinocerebellar ataxia.

ataxia with the exception of one SCA8 patient, who we identified as having parkinsonism at the initial visit. Various oculomotor abnormalities were the most common extracerebellar signs (86.3%), with saccadic slowing being the most prominent in SCA2 (90.3%) and SCA7 (71.4%), and vertical gaze-evoked nystagmus being prominent in SCA6 (73.7%). Parkinsonism was observed in early-stage SCA8 (25.0%), SCA3 (15.8%), and SCA2 (3.2%). Dopamine transporter (DaT) imaging was performed in three patients (one SCA2 and two SCA8), all of whom showed decreased DaT uptake. Blepharospasm, cervical dystonia, and/or oromandibular dystonia without any triggering drug history were most common in SCA8 (25.0%) and SCA3 (15.8%). Myoclonus was detected in SCA17 (100%), SCA8 (12.5%), SCA1 (7.7%), and SCA3 (5.3%), while chorea was identified in SCA8 (12.5%) and SCA2 (3.2%) patients. More than half of the patients with SCA7 (57.1%) complained of decreased visual acuity in the early stage; the visual disturbance had appeared before ataxia in three patients in whom ophthalmological examinations revealed macular degeneration. Pyramidal signs were most prominent in SCA7 (85.7%) and SCA1 (53.8%), and hyporeflexia was most common in SCA2 (38.7%) and SCA3 (18.4%). Dysautonomia was reported in 12 patients (10.3%) and was most common in SCA3 (21.1%). Dementia was reported in one patient with SCA6, one with SCA7, and one with SCA17. The SCA17 patient (100%) complained of memory disturbance, word-finding difficulties, and social withdrawal in her early 40s, and thus she was initially suspected of having early-onset Alzheimer's dementia. The bulging-eye signs were specific to SCA3 (10.5%). Video-oculography, nerve conduction studies, and autonomic

function tests were performed in 49 (41.9%), 35 (29.9%), and 46 (39.3%) patients, respectively; the results are presented in Supplementary Table 2 (in the online-only Data Supplement).

Brain MRI findings

MRI findings are presented in Table 2. Most of the patients (93.2%) exhibited cerebellar atrophy in the early stages of SCA, with the proportion of affected patients being lowest in SCA8 (75.0%). Involvement of the pons was frequent in SCA2 (93.5%) and SCA7 (71.4%), and was found in half of the patients with SCA1 and SCA3. However, only one patient with SCA8 (12.5%) demonstrated pontine atrophy, while none of the patients with SCA6 showed pontine atrophy. The one patient with SCA17 demonstrated vermian atrophy in which the volumes of the cerebellar cortex and pons were preserved. Hot cross bun (HCB) signs and MCP hyperintensities were rarely found, but they co-occurred in one SCA2 and one SCA8 patient. ICC values for MRI findings ranged from 0.905 to 1.000: 0.968 for cerebellar atrophy, 0.963 for vermian atrophy, 0.991 for pontine atrophy, 1.000 for HCB signs, and 0.905 for MCP hyperintensities.

DISCUSSION

This is the first report on an investigation of the combined clinical and MRI characteristics of very-early-stage SCA. This study found that the median disease duration at the initial visit was 2.6 years, which is significantly shorter than in previous studies,[6,10] and the severity of ataxia as assessed using the SARA score was relatively mild in our study. Some extracerebellar signs were specific to SCA subtypes, even in the early stage.

SCA3 is known to be the most prevalent subtype of SCA globally,[2] which is also the case in many Asian countries. One Chinese study found that the frequency of SCA3 was as high as 72.5%.[11] SCA3 has also been found to be the most frequent subtype in Singapore (41.7%),[12] Japan (43%),[13] and Taiwan (32%).[14] We observed that SCA3 was the most prevalent in the present cohort, while a previous Korean nationwide study found that SCA2 occurred most frequently.[15] However, the distribution of SCAs showed regional variations, and there was only a small difference between the numbers of SCA2 and SCA3 patients (27.9% vs. 23.1%) in that study.[15] Therefore, follow-up studies are needed to further clarify the distribution of SCA subtypes in the Korean population.

The age at onset for each SCA subtype in our Korean study was generally the same as those reported for other populations,[16,17] with the exception of SCA6. Although SCA6 is reported to be a late-onset type of cerebellar ataxia, the age at onset in the present study was 43.2±12.6 years (mean±standard deviation; median 41.6 years). Onset ages in European, USA, Japanese, and Chinese cohorts of 54.3±10.6, 52.2±10.3, 48.0±9.3, and 45.0±10.0 years, respectively, have been reported,[16-19] which suggests that a younger age at onset could be characteristic of SCA6 in Asian populations.

Most patients in this study complained of gait disturbance but did not require assistance (stage 0 or 1),[5] and the distribution of oculomotor findings was similar to that in a previous study.[10] Saccadic slowing was relatively specific to SCA2 and SCA7, and vertical gaze-evoked nystagmus was prevalent in SCA6. Square-wave jerks (SWJ) were prevalent among SCA3 patients in our cohort, while they were previously reported to be frequent in SCA2 and SCA17 patients.[10] Our result is supported by video-oculography findings in which SWJ were present even in the presymptomatic phase of SCA3 in a Chinese cohort.[20]

Parkinsonism has been reported in SCAs, especially in SCA2, SCA3, and SCA17.[21] In our study, parkinsonism was strictly defined as described above and its frequency was highest in SCA8, followed by SCA3, and relatively low in SCA2 patients. This may be due to several reasons. A previous study found that older age at onset (mean 45.8 vs. 26.9 years) and fewer CAG repeats (mean 36.2 vs. 43.1) were related to a parkinsonian phenotype in SCA2.[22] SCA2 patients in the present cohort were relatively younger at onset (mean 37.3 years, median 37.5 years) and had a moderate number of CAG repeats (mean 40.6, median 41.0), which may partially explain the low incidence of parkinsonism. Some patients demonstrate parkinsonism in the later stage of the disease,[23] and hence

Table 2. Magnetic resonance imaging findings at the initial visit

	SCA1 (*n*=13)	SCA2 (*n*=31)	SCA3 (*n*=38)	SCA6 (*n*=19)	SCA7 (*n*=7)	SCA8 (*n*=8)	SCA17 (*n*=1)	Overall (*n*=117)	*p**
Cerebellar atrophy	13 (100.0)	30 (96.8)	34 (89.5)	19 (100.0)	7 (100.0)	6 (75.0)	0 (0.0)	109 (93.2)	0.023
Vermian atrophy	13 (100.0)	30 (96.8)	30 (78.9)	19 (100.0)	5 (71.4)	4 (50.0)	1 (100.0)	102 (87.2)	0.001
Pontine atrophy	7 (53.8)	29 (93.5)	21 (55.3)	0 (0.0)	5 (71.4)	1 (12.5)	0 (0.0)	63 (53.8)	<0.001
HCB signs	0 (0.0)	2 (6.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (12.5)	0 (0.0)	3 (2.6)	0.200
MCP hyperintensities	0 (0.0)	2 (6.5)	0 (0.0)	0 (0.0)	1 (14.3)	1 (12.5)	0 (0.0)	4 (3.4)	0.108

Data are *n* (%) values.
*Data of one SCA17 patient were omitted.
HCB: hot cross bun, MCP: middle cerebellar peduncle, SCA: spinocerebellar ataxia.

parkinsonism might not be prominent in the early stage. Serial assessments may reveal if clinical characteristics change with disease progression. Furthermore, several studies have shown that patients with familial or sporadic parkinsonism are ultimately found to have SCA2 or SCA17.[21] It is possible that SCA patients with pure parkinsonism are not screened for SCAs, resulting in underdetection. It was particularly interesting that one SCA2 and two SCA8 patients in the present study exhibited predominant parkinsonism in the early stage and demonstrated decreased DaT binding with the delayed or mild expression of ataxia. The SCA2 patient and one of the two SCA8 patients showed levodopa responsiveness, and the SCA2 patient later suffered primarily from levodopa-induced dyskinesia. Only two of the six SCA3 patients with parkinsonism responded to levodopa.

Pyramidal signs were prevalent in SCA1 and SCA7, with frequencies similar to those found in the later stages of the disease.[24,25] Accordingly, we concluded that the brain regions that the pyramidal tract traverses are involved in the early stages of SCA1 and SCA7. Hyporeflexia was frequent in SCA2 and SCA3 patients in this cohort, while the overall frequency was lower than reported previously.[26,27] It is possible that the peripheral nerves of our patients were less affected due to them being in the early stages of the disease. Additionally, relatively few of the present patients underwent electrophysiological tests, and so peripheral neuropathy may have been underdetected.

Retinal degeneration is characteristic of SCA7, and visual symptoms can appear at any time during the disease course. Decreased visual acuity was most prevalent in SCA7 in this study, being observed in 57.1% of patients; however, this rate was lower than that reported for a study involving SCA7 patients from Africa, Europe, and Israel, where 83% showed decreased visual acuity at mean disease duration of 8 years.[24] The incidence of decreased visual acuity may increase as the disease progresses toward its later stages.

Dysautonomia has been reported in SCA patients,[28,29] but is not clinically significant in the early stage. Nevertheless, caution is needed since one-fifth of the SCA3 patients complained of autonomic dysfunction, which might be misdiagnosed as the cerebellar phenotype of multiple system atrophy.[30]

It seems that dementia is rare in early-stage SCAs, although cognitive decline has frequently been reported in SCA1, SCA2, SCA3, and SCA6.[31,32] Since the MMSE might not be sufficiently sensitive to detect the cognitive changes in early-stage SCA, the patients with mild cognitive impairment or cerebellar cognitive affective syndrome may have been underdetected in the present study. Furthermore, adjusting MMSE scores based on education status may lead to different results. Thus, we only focused on patients with dementia whose cognitive symptoms were sufficiently severe to interfere with their activities of daily living. It is important to perform follow-up investigations of multiple cognitive domains as the disease progresses. The bulging-eye signs were specific to SCA3 (10.5%) in this study, which is a significantly lower prevalence than that found in a Brazilian study (65.3%)[33] in which the mean disease duration was 9 years. Since longitudinal data regarding bulging-eye signs are lacking, it is not yet clear whether more patients will exhibit these signs as the disease progresses or if the interstudy difference is due to racial variations.

In terms of MRI findings, SCA1, SCA2, SCA3, SCA7, and SCA8 have been considered to be of the olivopontocerebellar atrophy (OPCA) type, and SCA6 as the cerebellar cortical atrophy (CCA) type. Early-stage MRI findings showed a pattern similar to those of the advanced stage in SCA2, SCA6, and SCA7; however, only 50% of SCA1 and SCA3 patients demonstrated the OPCA type, and most SCA8 patients exhibited the CCA type in the early stage. We could not characterize the MRI findings in SCA17 due to this being present in only one patient. MRI changes are associated with clinical features, but they were recognizable even at the initial visit when the median SARA score was lower than 10. This was not surprising given that structural and functional changes can be observed even in the preclinical stage.[34] Meanwhile, HCB signs and MCP hyperintensities were extremely rare in the early stage,[35] but a diagnosis of SCA2 or SCA8 might be considered when they are present.

Our clinical characterization of the SCA subtypes revealed some patients with absent or only mild ataxia. One SCA8 patient presented with parkinsonism without ataxia, and her symptoms were tolerable with levodopa. Since we had previously encountered nonataxic phenotypes, including parkinsonism and motor neuron disease in SCA8,[36] the mild cerebellar atrophy evident in her brain MRI led us to screen for SCAs. One SCA2 patient initially demonstrated segmental dystonia, with diagnostic clues provided by a family history of ataxia and accompanying mild dysmetria. There have also been previous reports of an SCA2 patient with focal dystonia[37] and SCA3 patients misdiagnosed as levodopa-responsive dystonia, Huntington's disease, or hereditary spastic paraplegia.[38,39] Since nonataxic features could be predominant in some cases, SCAs should be considered when those symptoms do not correspond to the known diagnoses.

We further investigated whether the presence of extracerebellar signs or MRI abnormalities was associated with the severity of ataxia as assessed using the SARA score. Some extracerebellar signs showed significant correlations with the SARA score in SCA1, SCA2, and SCA3 (Supplementary Table 3 in the online-only Data Supplement). However, the prevalence of extracerebellar signs may increase with disease pro-

gression, and so since the prevalence rate may vary from that indicated solely by changes in the SARA score, caution is needed when interpreting the results.

This study has several limitations. First, since the number of patients was small for each SCA subtype, their characteristics might not have been fully represented in this study. In particular, there was only one patient with SCA17, which may have been underdetected due to its clinical heterogeneity, including chorea, parkinsonism, and cognitive decline.[40] The SCA17 patient was excluded from the statistical analyses, and so future studies are needed to improve the robustness of the clinical characterization performed in the present study. Second, the identified extracerebellar signs were mostly based on neurological examinations. The findings of electrophysiological tests were available for only in small proportion of patients, making it difficult to interpret the results. Nevertheless, these clinical data were organized on a unified case-report form in order to improve the standardization. Third, the age at onset may have been inaccurate since it was based on the patients' own descriptions in their medical records. A previous study that investigated the first symptom of SCAs also utilized patient-reported ages at onset, in which the patients' initial visits took place after a disease duration of approximately 10 years. In the present study, patients visited our center at a median of 2.6 years after the initial symptom had manifested; thus, we believed that it was possible to approximate the disease duration and evaluate the early-stage findings.

In conclusion, this novel study investigated various extracerebellar signs of early-stage SCAs in the Korean population, some of which were characteristic of specific SCA subtypes. Recent studies have introduced molecular biomarkers[41,42] and potential therapeutic targets in SCAs,[43] and so characterizing early-stage findings will not only facilitate early diagnosis but may also provide patients with more treatment options.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.3988/jcn.2021.17.2.242.

Author Contributions

Conceptualization: Ji Sun Kim, Jin Whan Cho. Data curation: Minkyeong Kim, Jin Whan Cho, Jun Kyu Mun, Eun-Hyeok Choi. Formal analysis: Minkyeong Kim, Ji Sun Kim, Jin Whan Cho. Methodology: Minkyeong Kim, Ji Sun Kim, Jin Whan Cho. Writing—original draft: Minkyeong Kim, Ji Sun Kim. Writing—review & editing: all authors.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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All procedures in studies involving human participants were performed in accordance with the ethical standards of the Institutional Review Board of the Samsung Medical Center, Seoul, Korea (#2019-03-016) as well as with those of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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