

Autosomal Dominant Cerebellar Ataxia among patients of the Asahikawa Medical Center in Hokkaido

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Abstract

Object The occurrence of autosomal dominant cerebellar ataxia (ADCA) differs widely by location worldwide. The aim of this study was to assess the prevalence of ADCA subtypes among patients of Asahikawa Medical Center in Hokkaido.

Patients and Methods This study was performed from July 2012 to June 2015. PCR and/or direct sequencing were carried out for 50 participants who were each clinically diagnosed with spinocerebellar ataxia (SCA).

Results Among the 50 participants, 25 had familial SCA, and 25 had sporadic SCA. SCA6 was the most common type identified, found in 14 (43.8%) cases among 32 genetically confirmed cases. SCA6 was followed by SCA1, SCA31, and dentatorubral-pallidoluyian atrophy (DRPLA), which each accounted for four (12.5%) of the 32 cases. SCA7 and SCA17 were not detected in this study. Two SCA6 patients were homozygous for a 21-CAG repeat allele, and each presented with early onset, pure cerebellar ataxia. Among the 25 sporadic patients, 11 cases (44%) was clarified one case with SCA1, six SCA6, one SCA8, one SCA31, and two DRPLA. Notably, 18 participants could not be classified into an SCA type.

Conclusion This study reveals the prevalence of ADCA in Asahikawa Medical Center. It is important to correctly diagnose the SCA subtype of each for effective counseling, management of therapy, and understanding of prognosis.

Key words: Asahikawa, autosomal dominant cerebellar ataxia, SCA6, homozygous, SCA31

Introduction

Autosomal dominant cerebellar ataxia (ADCA), genetically defined as spinocerebellar ataxia (SCA), is characterized as progressive ataxia with variable degrees of extracerebellar symptoms. Harding proposed that ADCA could be clinically divided into three categories, Type I, Type II, and Type III¹⁾. However, we prefer a genetic classification based upon associated SCA loci. Notably, the number of newly identified SCA types is growing, and SCA1 through SCA40 are currently recognized. Genetic abnormalities associated with this condition are variable and include repeat expansions in coding and noncoding regions of target genes, conventional mutations, and large gene rearrangements. Each genetic disorders can result in neuronal cell death due to toxic gain-of-function or loss-of-function mechanisms. Several published studies have reported that the frequency of ADCA varies among different regions of Japan. To understand the etiology of SCA, we investigated the prevalence of SCA at Asahikawa Medical Center, Asahikawa, Hokkaido.

Patients and methods

Patients

This study was performed from July 2012 to June 2015. A total of 50 patients (23 males and 27 females) with ataxia were enrolled in this study. The familial SCA patients are determined that there are progressors in family history. On the other hand, the sporadic SCA patients are showed cases that unable to confirm proband. This study was approved by the Ethics Committee of Matsue Medical Center. Informed consent was obtained from each participant prior to the study. Magnetic resonance imaging (MRI) was performed using a 1.5 T MR scanner, and axial T1 weighted, T2 short T inversion recovery (STIR), and fluid-attenuated inversion recovery (FLAIR) images were generated for each patient.

Genetic analysis

Blood samples were obtained from each patient, and samples were used for molecular genetic analysis. Genomic DNA was isolated from peripheral blood lymphocytes by a standard phenol/chloroform method. The presence of mutations related to SCA1, SCA2, SCA3, SCA6, SCA7,

SCA8, SCA17, or DRPLA were assessed by polymerase chain reaction (PCR) amplification with primer pairs, as described by Mori et al.³⁾ Additionally, the PCR-RFLP (restriction fragment length polymorphism), method was used to screen for mutations in the SCA31 gene⁴⁾.

Results

Blood samples were collected from each of the 50 participants who together represented a total of 46 families; 25 patients (6 males and 15 females from 19 different families and 10 males and 15 females from 21 different families) had familial SCA, and the other 25 patients (13 males and 12 females representing 25 different families) had sporadic SCA. The sex ratio, mean age at onset, number of family members, and mean disease duration of the 50 participants from the 46 families are listed in Table 1. Mean age at onset and mean disease duration were 43.8 ± 15.6 years and 16.0 ± 8.4 years, respectively, for the familial cases and 49.6 ± 14.4 years and 13.2 ± 8.1 years, respectively, for the sporadic cases. Table 2 summarizes the results of the genetic analysis. Twenty one individuals from 19 families had familial SCA (9 males and 12 females), and 11 individuals (6 males and 5 females) from 11 families had sporadic SCA. All patients were Japanese. SCA6, which causes a polyglutamine disorder due to an expanded CAG repeat in *CACNA1A*, was the most common, accounting for 14 (43.8%) of the 32 cases. Of 14 patients with SCA6 (the 14 SCA6 patients), two were homozygous for a 21-repeat expansion; age at disease onset was 48 years old for one patient and 58 years old for the other. The second most common were SCA1, SCA3, and DRPLA, accounting for four cases each. Of the 50 participants, four familial SCA patients and 14 sporadic SCA patients could not be classified into an SCA type.

Figure 1 shows the relationship between the age of

Table 1 Sex ratio, mean age at onset, and mean disease duration among the present cases. Mean age of onset and mean disease duration is showed by mean \pm SD.

	Familial cases	Sporadic cases
Number of families	21	25
Number of cases	25	25
Sex ratio (M/F)	10 / 15	13 / 12
Mean age at onset (Y)	43.8 ± 15.6	49.6 ± 14.4
Mean disease duration (Y)	16.0 ± 8.4	13.2 ± 8.1

Table 2 Results of a genetic analysis examining 50 cases of spinocerebellar ataxia
The numbers in parenthesis shows percentage of each disorder among all diagnosed cases.

Disease name	Familial		Sporadic	Total cases (%)
	Family numbers	Cases (%)	Cases (%)	
SCA1	3	3	1	4 (12.5)
SCA2	1	1	0	1 (3.0)
SCA3	2	2	0	2 (6.3)
SCA6	7	8	6	14 (43.8)
SCA7	0	0	0	0 (0)
SCA8	2	2	1	3 (9.4)
SCA17	0	0	0	0 (0)
SCA31	2	3	1	4 (12.5)
DRPLA	2	2	2	4 (12.5)
Number of diagnosed cases	-	21(84)	11 (44)	32 (64)
Number of undiagnosed cases	2	4 (16)	14 (56)	18 (36)
Total numbers	21	25	25	50

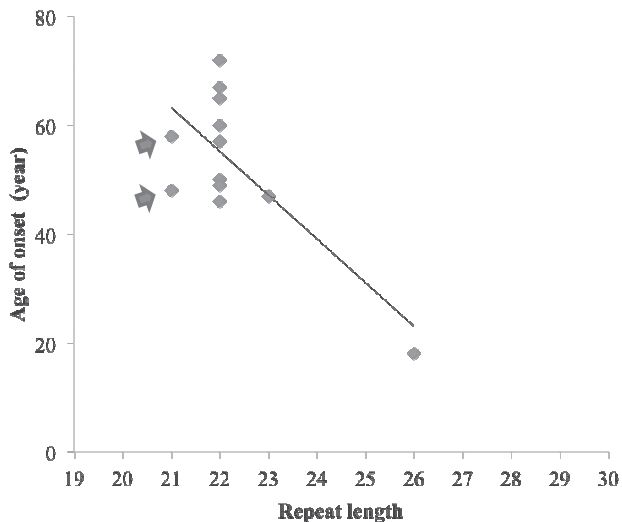


Figure 1 Relationship between age of onset and CAG repeat length at expanded alleles in affected individuals ($n=14$, $R^2=0.55$). The regression line is $Y=-8.05X+232.2$ (where Y represents age of onset and X represents repeat length). The cases involving homozygous SCA alleles are indicated by an arrow.

onset and the CAG-repeat length in the expanded alleles in affected individuals. An inverse correlation ($n=14$, $R^2=0.55$) was noted between the length of CAG repeats and the age of onset for individuals affected by SCA6. Of the two individuals with homozygous 21-repeat expansions in SCA6, one was a 68-year-old female who developed the condition at 48 years of age, and the other was a 76-year-old female who developed the condition at 58 years of age.

However, no family history of ataxia was reported for the latter, and genetic analysis was not performed. Interestingly, age of onset is wide range from 46-year-old to 72-year-old in 22-repeat expansions in SCA6.

SCA8 expansions were detected in three individuals from three different families. One patient was a 75-year-old female who developed the condition at 65 years of age and had a 126-repeat expansion. Other SCA8 patients (a 79-year-old and a 50-year-old female) developed the condition in their 20s. The two had comparable expansions of 123 repeated units and 142 repeated units, respectively. In addition, the 50-year-old female with SCA8 had a left trigeminal schwannoma.

Four individuals from three different families were each found to possess a SCA31 repeat expansion. One was a 79-year-old female (59 years old at disease onset) who had an 4.0 kb insertion that contained a $(TGGAA)_n$ stretch. Her brother and uncle each had ataxia, though neither participated in the genetic analysis. Another two cases were a 79-year-old male and his 68-year-old brother who each had an $(TGGAA)_n$ insertion; one was 3.4 kb long, and the other was 3.1 kb. The remaining case was a 65-year-old male with a sporadic case of ADCA.

Of the 11 sporadic SCA patients, six were due to SCA6, two were due to DRPLA, and one case each was due to SCA1, SCA8, or SCA31. In this study, there were no cases associated with SCA7 or SCA17.

Discussion

In the present study, we performed a genetic analysis of patients with SCA and investigated the prevalence of ADCA in the area around the Asahikawa Medical Center. The findings demonstrated that SCA6 was the most common form of SCA. In addition, SCA1, SCA31, and DRPLA were equally the second most common forms of SCA. In the study, we demonstrated that there were cases which could be diagnosed with familial SCA even if sporadic SCA patients. It is expected that precise genetic diagnose lead to appropriate genetic treatments in the future.

In Japan, the frequency of ADCA varies among several areas^{3, 5, 6, 7}. Recent reports from other districts of Japan demonstrate that SCA3, SCA 6, and DRPLA are prevalent. In Japan, SCA31 is diagnosed based on disease-specific insertions of penta-nucleotide (TGGA)_n repeats in SCA31-critical lesions upstream of *PLEKHGA4*, and it has been defined as a fourth subtype of ADCA⁴. Surprisingly, SCA31 is the predominant subtype of ADCA in Nagano. In Nagano, approximately 42% of ADCA families have SCA31⁸. Four out of the 32 participants identified with an SCA type (12.5%) were found to have with SCA31 in the current study. SCA6 and SCA31 are each subtypes of ADCA characterized by adult-onset and pure cerebellar ataxia; moreover, clinical features of these conditions are very similar. Consequently, it can be difficult to accurately diagnose these conditions. To address this, Sakakibara et al. showed that SCA31 patients, unlike SCA6 patients, had hearing loss and that MRI findings differed between SCA31 and SCA6; specifically, cerebellar atrophy starts from the upper vermis in SCA31 patients, whereas the fourth ventricle with middle cerebellar peduncle atrophy becomes enlarged in SCA6 patients, even at the early stage of disease onset⁹. The MRI findings of our study (data not shown) were similar to those of Sakakibara et al. These differences between SCA6 and SCA31 in brain images might play a key role in accurate diagnosis, although genetic analysis is also very important for distinguishing between SCA6 from SCA31.

SCA6 is caused by a small expansion of CAG repeats

in the *CACNA1A* gene, which codes for an α_{1A} -voltage-dependent calcium channel subunit, and belongs to a group of CAG triplet repeat diseases that include SCA1, SCA2, Machado-Joseph disease (MJD)/SCA3, SCA7, SCA12, and DRPLA¹⁰. Normal *CACNA1A* alleles have 4 to 18 repeats, whereas expanded alleles in patients with SCA6 have 20 to 29 repeats. Many published reports show that CAG-repeat length is loosely related to the age of onset. For example, Mariotti et al. described cases involving homozygous SCA6 alleles with intermediate-sized 19-repeat expansions¹¹. In addition, Komeichi et al. described two sibs with SCA6 who were both homozygous for 20-repeat alleles¹²; however, neither of the parents developed ataxia. We examined two patients from different families who were both homozygous for a 21-repeat expansion in SCA6 and found that one patient had an earlier age of onset (48 years old). In 22-repeat expansion in SCA6, we showed that there is wide range of onset age from 47 to 72-year-old. Whether changes in gene dosage caused gain-of-function or loss-of-function was unclear; nevertheless, our results suggested that the dosage of the CAG repeats expansion played some role in phenotypic expression of SCA6.

SCA8, classified as type I ADCA, is characterized by a slow progressive, predominantly cerebellar ataxia, cognitive dysfunction, pyramidal and sensory signs, and a variable age at onset. Marked cerebellar atrophy is found on MRI or CT scans^{13, 14}. Therefore, it can be difficult to clinically discriminate SCA8 from the other SCAs, similar to our three cases in the present study. First described in 1999¹⁵, SCA8 is known to be associated with CTG/CAG repeat expansion in the ataxin 8 gene on chromosome 13q21. The pathogenesis of SCA8 is thought to result from RNA-mediated neurotoxicity that is similar to what causes myotonic dystrophy type I¹⁶.

In conclusion, we determined the prevalence of SCA subtypes among ADCA patients at Asahikawa Medical Center. This study verified the existence of genetically identifiable SCA subtypes among patients with sporadic ADCA. It is important to correctly diagnose the SCA subtype of each for effective counseling, management of therapy, and understanding of prognosis.

Conflict of Interest

The authors state that they have no conflict of interest.

Acknowledgements

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