The Parkinsonian Phenotype of Spinocerebellar Ataxia Type 2

Chin-Song Lu, MD; Yah-Huei Wu Chou, PhD; Pei-Chi Kuo, BS; Hsiu-Chen Chang, BS; Yi-Hsin Weng, MD

Background: We recently reported that spinocerebellar ataxia type 2 (SCA2) caused familial parkinsonism in 2 brothers with predominant symptoms of resting tremor, rigidity, and bradykinesia that responded to levodopa.

Objective: To investigate SCA2 as the possible cause of familial parkinsonism in our series and subsequently to analyze the correlation between the clinical manifestation and CAG repeat size in the ataxin-2 gene product.

Patients: One hundred thirty patients from 41 families with familial parkinsonism were examined for SCA2. Another 8 patients with the classic ataxic phenotype of SCA2 from 6 families were the control group.

Design: The length of expanded CAG repeat was analyzed by means of polymerase chain reaction. The clinical data and genetic findings in the parkinsonian phenotype were then compared with those in the ataxic phenotype.

Results: We found expanded CAG repeats in the ataxin-2 gene product in 7 patients from 4 families with parkinsonism, which was about 10% of our familial parkinsonism series. The parkinsonian phenotype was characterized by resting tremor, rigidity, and bradykinesia. Only mild dysarthria, ataxic gait, and instability were noted, particularly in the late stage. Patients with the parkinsonian phenotype had an older mean±SD age of symptom onset (45.8±13.9 years) and shorter mean±SD abnormal CAG length (36.2±1.1 repeats) than did those with the ataxic phenotype (26.9±11.0 years and 43.1±3.2 repeats). Parkinsonian SCA2 responded well to levodopa.

Conclusions: We conclude that SCA2 is a minor cause of familial parkinsonism, particularly in Taiwan. The parkinsonian phenotype is associated predominantly with a shorter abnormal range of CAG repeat lengths and older onset age. Because of the clinical resemblance among familial parkinsonisms, we suggest that SCA2 should be excluded in cases of familial parkinsonism.

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PINOCEREBELLAR ATAXIA TYPE 2 (SCA2) is caused by expansion of a CAG trinucleotide repeat in the coding region of the ataxin-2 gene product located on chromosome 12q23-24.1.1-4 The normal range of the CAG repeat usually extends from 14 to 31 repeats, and it ranges from 34 to 200 or more in affected persons.2,6 A range of 32 to 33 CAG repeat alleles is considered indeterminate.7 The clinical features are usually cerebellar gait and limb ataxia, dysarthria, slow saccades, and decreased tendon reflexes; however, a full phenotypic spectrum cannot be determined because of the wide variation in phenotypes.8,11 The abnormal length of CAG repeats correlates inversely with age at symptom onset and directly with severity of observations, such as cerebellar gait and limb ataxia, slow saccades, and hyporeflexia.5,6,8-11 The longer repeats are also associated with more rapid disease progression. Small increments in repeat size had a large effect on onset age. Pathological findings frequently reveal severe neuronal loss in the pons and cerebellum and marked degeneration in the substantia nigra, inferior olive, and dorsal columns.8-10 However, clinical signs are difficult to correlate with pathological findings.10

Parkinsonism as a dominant clinical phenotype has rarely been described in patients with SCA2.5,11 Cancel et al7 reported a parkinsonian syndrome in 16 of 111 patients, which showed a correlation with the duration of disease with SCA2 but not with CAG repeat length. However, no further detailed information was provided. Schols et al12 described a patient with SCA2 who had bradykinesia and marked rigidity, with onset age of 12 years and 52 CAG repeats, which was the earliest onset age and largest number of repeats in their series of 21 patients. On the other hand, Sasaki et al13 reported parkin

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sonism in 2 of 28 patients from 8 Japanese families with SCA2. For 1 of the 2 patients, clinical and CAG repeat data were not available. The other patient was a man who had homozygous SCA2 alleles with 39 CAG repeats and initially had unstable gait at age 38 years. Later, at age 52 years, a masklike face and rigidity were found, in addition to scanning speech, gait and limb ataxia, saccadic pursuit, and partial response to levodopa.

Gwinn-Hardy et al recently described a Chinese family with SCA2 who manifested a parkinsonian phenotype with mild ataxia and slow saccades. Two of 8 affected members were particularly noteworthy: 1 had 36 CAG repeats, a phenotype of typical Parkinson disease (PD) beginning at age 38 years, and a dramatic response to levodopa. The other, who had 35 CAG repeats, had atypical parkinsonism beginning at age 43 years and developed levodopa-induced dyskinesias. Authors of a subsequent article described a similar parkinsonian phenotype in 2 patients from 2 other Chinese families. Both families had typical PD with late onset at age 50 years and response to levodopa, and they had 36 and 37 CAG repeats. We described 2 similar patients in another Taiwanese family. The importance of the role of the parkinsonian phenotype of SCA2 that causes familial parkinsonism in Chinese is the subject of this study.

METHODS

The length of CAG repeats on the allele of the ataxin-2 gene product was determined in a series of 130 patients from 41 families with familial parkinsonism who were referred to the Movement Disorders Unit of the Department of Neurology at Chang Gung Memorial Hospital (Taipei, Taiwan). At least 2 affected persons in each family responded to levodopa. The mode of inheritance was presumed to be autosomal dominant in 26 families with affected persons in only 1 generation. The possibility of mutations in the α-synuclein gene and the parkin gene was excluded by using single-strand conformational polymorphism and DNA sequence analysis. Screening results for abnormal CAG repeats of spinocerebellar ataxia type 3 were negative.

For analyzing CAG size in ataxin-2, 20 mL of blood was drawn from affected and nonaffected family members after informed consent was obtained from each subject. These blood samples were then layered onto Ficoll-Paque Plus (Amersham Biosciences AB, Uppsala, Sweden) to separate lymphocytes for later use. We extracted genomic DNA from 1 aliquot of lymphocytes by using a standard method. For SCA2 allele analysis, a region containing the CAG repeat in the SCA2 gene was amplified with a polymerase chain reaction with modified conditions previously described. Three milliliters of the amplified polymerase chain reaction products was then mixed with 2 mL of gel loading buffer with formamide, boiled for 2 minutes, and analyzed on 6% polyacrylamide DNA sequencing gels in parallel with an M13 sequencing ladder. Gels were then dried and subjected to autoradiography for 10 to 16 hours at room temperature. From our database, clinical information and abnormal CAG size were also obtained in 8 patients from 6 families with the classic ataxic phenotype of SCA2; they were the control group. The t test was used for statistical analysis of the abnormal CAG repeat size and onset age between the 2 phenotypes; P<.05 was considered significant.

RESULTS

The demographic data in 15 patients with SCA2 from 10 families with autosomal dominant inheritance are summarized in the Table. Ten patients from 3 families with autosomal dominant parkinsonism and 1 family with autosomal recessive parkinsonism were affected (Figure 1). Clinical data were available in 7 patients with a parkinsonian phenotype; patients 4 and 5 were described previously.

The mean±SD onset age was 45.8±13.9 years (range, 34-69 years), and the mean±SD CAG repeat number was 36.2±1.1 repeats (range, 35-38 repeats) in the 7 patients with the parkinsonian phenotype. In contrast, the mean±SD onset age was 26.9±11.0 years (range, 12-44 years), and the mean±SD CAG repeat number was 43.1±3.2 repeats (range, 40-48 repeats) in the 8 patients with the classic ataxic phenotype. There were significant differences in both the number of CAG repeats (P<.001) and onset age (P<.05) between the parkinsonian and ataxic phenotypes (Figure 2). However, the mean duration of illness was similar; mean±SD 12.6±11.8 years (range, 2-35 years) and 14.3±5.8 years (range, 4-24 years) in the parkinsonian and ataxic phenotypes, respectively.

In the parkinsonian phenotype, bradykinesia and rigidity appeared in all 7 patients, but resting tremor was seen in only 3. The parkinsonian symptoms were relatively symmetrical, although 2 patients started with unilateral tremor; patient 5 had right hand tremor, patient 7 had left limb tremor. In the late stage, mild dysthria was noted in 5 patients, mild ataxic gait in 3, and limb ataxia in 2. Anticipation of earlier onset age in the younger generation was confirmed in the child of 1 parent-child pair with a parkinsonian phenotype (patients 1 and 2). A sustained good response to levodopa was noted in 6 patients with parkinsonian SCA2 (range, 150-1300 mg daily). Motor scores on the Unified Parkinson’s Disease Rating Scale improved from 40 to 25, 35 to 21, 45 to 30, and 28 to 12, respectively, in patients 2, 3, 6, and 7. Levodopa had not been prescribed in the patients with ataxic SCA2. On the other hand, patients with an ataxic phenotype predominantly had cerebellar gait and limb ataxia, slow saccades, ataxic dysthria, intention tremor, hypotonia, hyporeflexia, and tendency to fall. None had any parkinsonian features. Also, these patients more frequently had orofacial fasciculation, eyelid retraction, chorea, and dystonia than did those with the parkinsonian phenotype (Table).

COMMENT

In a series of 130 patients with familial parkinsonism, we found 10 from 4 families with SCA2. Autosomal dominant inheritance was presumed in 3 families and autosomal recessive inheritance in 1 family (family II in Figure 1 and the Table). However, we could not trace the ancestors adequately in the family with autosomal recessive inheritance. Therefore, patients with familial parkinsonism with autosomal dominant inheritance should be particularly aware of SCA2 as the possible cause of the parkinsonism. Seven of these 10 patients had a parkinsonian phenotype, in contrast to the control group of 8 patients from 6 families who had the ataxic phenotype, as recorded in our database. The difference in clinical manifestation between these 2 phenotypes of SCA2 is clear (Table). There were only a few overlapping symptoms, such as dysthria and postural instability. Patients with the par-
Kinensive phenotype manifested typical aspects of PD without obvious cerebellar signs, particularly in the early stage. However, the relatively symmetrical manifestation of their parkinsonian symptoms is different from that of typical PD. The parkinsonian symptoms responded to levodopa, and drug-induced dyskinesia was observed, as was reported by Gwinn-Hardy et al.13

The 4 families with SCA2 with a parkinsonian phenotype were about 40% of our 10 families with SCA2. This relatively high prevalence is probably because of the small number of families. Nevertheless, the parkinsonian phenotype was not mentioned in 2 previous articles concerning SCA2 in Chinese.13,17 We speculate that if one performs genetic analysis for SCA2 only in families with an ataxic phenotype, families with SCA2 with a parkinsonian phenotype might never be discovered. Although SCA2 with a parkinsonian phenotype accounts for a minority of about 10% of familial parkinsonism cases in our database, it is important to remember the SCA2 cause in examining a patient with typical PD with other affected members in the family.

The parkinsonian phenotype has not been reported in other groups, such as those in Cuba1,8,9 and the United States,2,4 but is seen occasionally in German5 and Japanese6 populations. Spinocerebellar ataxia type 2 was reported in other groups, such as those in Cuba1,8,9 and the United States,2,4 but is seen occasionally in German5 and Japanese6 populations. Spinocerebellar ataxia type 2 was not found in a recent article about the screening of expanded CAG repeats in the ataxin-2 gene product in 270 patients who had levodopa-responsive parkinsonism and were of mixed ethnicity, including African American, Ashkenazi Jewish, Bengalese, European, and Hispanic origins.18 Until now, most such studies, including this one, were from Taiwan.13,15 The possibility of there being an ethnic predisposition for the parkinsonian phenotype needs to be explored further.

The parkinsonian phenotype in our SCA2 series was associated with a lower abnormal range of CAG repeats (<39) and later onset age, in contrast to the higher number of abnormal CAG repeats and earlier onset age for the ataxic phenotype. Authors of 2 previous articles documented a low abnormal range of CAG repeats and late-onset parkinsonian symptoms.13,14

Positron emission tomography revealed profound loss of F-dopa uptake bilaterally in the putamen and caudate nucleus in 2 patients with SCA2 with a parkinsonian phenotype.14 Similar to findings in patients with PD, the binding of technetium Tc 99m–TRODAT-1 in the striatum was markedly reduced, most severely in the putamen.15 This finding indicates that dopamine transporter activity, which corresponds to the integrity of dopamine neurons, was markedly impaired in those with parkinsonian phenotype SCA2.15

The parkinsonian features of parkinsonian phenotype SCA2 were characterized by (1) late age at onset of symptoms; (2) slow progression; (3) bradykinesia and rigidity, which were more frequent than was resting tremor; (4) good response to levodopa; and (5) mild postural instability in the late stages. From the clinical mani-

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Abbreviation: SCA2, spinocerebellar ataxia type 2.

*0 Indicates the individual was tested and SCA2 was absent; 1, mild findings or response; 2, moderate findings or response; 3, marked findings or response; 4, severe findings or response.
†Patient died.
‡NT indicates unknown or the individual could not be tested; plus sign, levodopa response.
§Levodopa-induced kinesia.
| Number of trinucleotide repeats contained in the ataxin-2 gene product. | | | | | | | | | | | | | | |

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cases, the parkinsonian phenotype persisted with-ultimately develop. After long-term observation in a few sitional form, in which full cerebellar symptoms will ul-

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Author contributions: Study concept and design (Drs Lu and Weng); acquisition of data (Dr Wu Chou and Kuo); drafting of the manuscript (Drs Lu, Kuo, Chang, and Weng); critical revision of the manuscript for important intellectual content (Dr Wu Chou); statistical expertise (Dr Chang); obtained funding (Drs Lu and Wu Chou); study supervision (Dr Lu).

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SCA2 as the cause in any familial parkinsonism in which the genetic defect is unknown.

We conclude that SCA2 should be considered a rare cause of familial parkinsonism. This parkinsonian phe- notype SCA2 is associated with late onset age and low abnormal size of the CAG repeat. We suggest that those with familial parkinsonism, even with typical PD manifestation and levodopa responsiveness, should undergo screening for SCA2.

REFERENCES


Figure 1. Pedigrees of 4 families with parkinsonian phenotype spinocerebellar ataxia type 2. Circles indicate females; squares, males; black symbols, affected family members; slashed symbols, deceased family members. Numbers in the right lower corner indicate the patient number from the Table. Family II has autosomal recessive inheritance, and the other 3 have autosomal dominant inheritance.

Figure 2. Onset age plotted against number of CAG repeats in patients with spinocerebellar ataxia type 2 (SCA2) with parkinsonian phenotype and ataxic phenotype. There is an inverse correlation between onset age and abnormal number of CAG repeats in all patients with SCA2 ($y = -0.22x + 48; r^2 = 0.63039$).


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SCA2 as the cause in any familial parkinsonism in which the genetic defect is unknown.

We conclude that SCA2 should be considered a rare cause of familial parkinsonism. This parkinsonian phe- notype SCA2 is associated with late onset age and low abnormal size of the CAG repeat. We suggest that those with familial parkinsonism, even with typical PD manifestation and levodopa responsiveness, should undergo screening for SCA2.

REFERENCES
