

Phenotype variability and early onset ataxia symptoms in spinocerebellar ataxia type 7: comparison and correlation with other spinocerebellar ataxias

Variabilidade fenotípica e ataxia de início precoce na ataxia spinocerebelar tipo 7: correlações com outras ataxias espinocerebelares

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ABSTRACT

The spinocerebellar ataxias (SCA) are a group of neurodegenerative disorders characterized by heterogeneous clinical presentation. Spinocerebellar ataxia type 7 (SCA7) is caused by an abnormal CAG repeat expansion and includes cerebellar signs associated with visual loss and ophthalmoplegia. Marked anticipation and dynamic mutation is observed in SCA7. Moreover, phenotype variability and very early onset of symptoms may occur. In this article, a large series of Brazilian patients with different SCA subtypes was evaluated, and we compared the age of onset of SCA7 with other SCA. From the 26 patients with SCA7, 4 manifested their symptoms before 10-year-old. Also, occasionally the parents may have the onset of symptoms after their children. In conclusion, our study highlights the genetic anticipation phenomenon that occurs in SCA7 families. Patients with very early onset ataxia in the context of a remarkable family history, must be considered and tested for SCA7.

Keywords: spinocerebellar ataxias, SCA, spinocerebellar ataxia type 7, genetic anticipation, early onset ataxia.

RESUMO

Ataxias espinocerebelares (SCA) são um grupo de doenças neurodegenerativas caracterizadas por expressão clínica variável. A ataxia espinocerebelar tipo 7 (SCA7) é causada por uma expansão anormal dos trinucleotídeos CAG, e clinicamente se caracteriza por sinais cerebelares associados a perda visual e oftalmoplegia. Antecipação genética e mutação dinâmica são frequentemente observados na SCA7. Além disso, podem ocorrer variabilidade fenotípica e início precoce dos sintomas. Neste artigo avaliamos uma série de pacientes brasileiros com diferentes subtipos de SCA, e comparamos a idade de início dos pacientes com SCA7 com outras SCA. Dos 26 pacientes com SCA7, 4 iniciaram os sintomas antes dos 10 anos de idade. Além disso, ocasionalmente, os pais podem ter o início dos sintomas após os mesmos se manifestarem nos seus filhos. Concluindo, esse estudo destaca o fenômeno da antecipação genética que ocorre em famílias com SCA7. Além disso, em pacientes com ataxia com início muito precoce no contexto de uma história familiar positiva, deve ser considerado o teste genético para SCA7.

Palavras-chave: ataxias espinocerebelares, SCA, ataxia espinocerebelar do tipo 7, antecipação genética, ataxia de início precoce.

Spinocerebellar ataxias (SCA) are a group of genetically defined autosomal dominant neurodegenerative disorders, characterized by heterogeneous clinical presentation^{1,2,3,4}. SCA may present with a broad combination of cerebellar syndrome and extracerebellar signs, which depends on the subtype^{5,6}. Up to now, 37 SCA subtypes have been described⁶.

Spinocerebellar ataxia type 7 (SCA7) is caused by a CAG expansion in the *ATXN7* gene, which is located at chromosome 3p12-p21.1. Normal alleles contain 4-35 CAG repeats, whereas pathological alleles for SCA7 contain from 36-306 CAG repeats⁷. Besides cerebellar signs, the main neurological manifestations of SCA7 include visual loss,

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Conflict of interest: There is no conflict of interest.

Received 15 May 2014; Received in final form 20 September 2014; Accepted 09 October 2014.

due to macular changes, cone dysfunction, retinal pigmentary dystrophy and ophthalmoplegia^{8,9,10}. Interestingly, in SCA7 patients, visual symptoms often may precede the onset of ataxic symptoms. In general, SCA patients have adulthood onset, although sporadic reports have demonstrated a very early onset of ataxia symptoms. Marked anticipation and dynamic mutation caused by intergenerational repeat instability with a bias toward expansion makes SCA7 the most unstable of the polyglutamine diseases^{4,11,12,13}. Instability of the repeat sequence (around 12 CAG/transmission) accounts for the marked anticipation of approximately 20 years/generation. Therefore, sporadic reports of very early onset of SCA7 ataxia are supposed to occur¹².

In this article, a large series of Brazilian patients with different SCA subtypes was evaluated, and we compared the age of onset and disease duration of SCA7 with other SCA. Furthermore, a detailed clinical description of the SCA7 patients is provided, aiming to demonstrate the wide phenotypic variability of this single genetic entity.

METHOD

We evaluated 166 patients, with different SCA subtypes at the Ataxia Unit, *Universidade Federal de São Paulo*, from February 2008 to December 2013. The patients were genetically tested and we obtained the following results: 18 had SCA1, 18 had SCA2, 91 had SCA3, 10 had SCA6, 26 had SCA7 and 3 had SCA10. All SCA patients were evaluated for the following demographic and clinical features: age at onset of ataxia symptoms, age at onset of visual symptoms, disease duration, CAG repeat length, duration of ataxia symptoms, duration of visual symptoms, presence of ophthalmoplegia and ataxia severity. The age at onset was determined by the year of the ataxia symptoms or by the year of visual complaints. Particularly in children, this was reported by the parents. There was no selection bias for age at onset, since all familial ataxias are evaluated in our division. In order to record ataxia severity, we used the Scale for the Assessment and Rating of Ataxia (SARA)

and the International Cooperative Ataxia Rating Scale (ICARS).

Statistical analysis

Statistical analysis was performed using Statistical Package for the Social Science version 17. To compare age of onset of ataxia and disease duration among SCA subtypes, we used one-way analysis of variance (ANOVA). Differences were considered significant when p was less than 0.05. For specific statistical analysis of the SCA7 patients we used the Mann-Whitney test for continuous variables and test for equality of proportions for categorical variables. In order to analyze the anticipation phenomenon, SCA7 patients were divided in two groups: age at onset of symptoms (visual impairment or ataxia) earlier or later than the transmitting parent.

RESULTS

Regarding SCA subtypes, SCA3 and SCA6 patients had later symptoms onset than SCA7 patients (Table 1 and Figure). From the 26 patients with SCA7, 4 manifested their symptoms before 10-year-old: 2 of them had ataxia and the other 2 had visual loss as the first manifestation. Moreover, 3 of them had inheritance from the mother. There was no patient with symptoms onset before 10-year-old in SCA1, SCA2, SCA3, SCA6 and SCA10. From all 26 SCA7 patients, 2 had the onset of ataxia symptoms after the disease had already been manifested in their children. These 2 patients had a later onset of neurological symptoms, after 50-year-old and had no visual symptoms. This phenomenon was not observed in the other SCA evaluated.

Specific clinical data analysis of SCA7 patients is shown in the Table 2, which describes the comparison of patients with age at onset of symptoms earlier and later than the transmitting parent for continuous variables. In the group of patients with age at onset of symptoms earlier than the transmitting parent, CAG repetition length was longer when compared with patients with age of symptoms onset

Table 1. Comparison of age of onset of ataxia symptom of each SCA subtype.

Age of onset of ataxia symptom	SCA7	SCA1	SCA2	SCA3	SCA6	SCA10
Media	27.85	35.39	28.06	36.91	48.20	47.00
Median	25.5	34.5	27.0	35.0	48.5	47.0
SD	15.32	10.53	11.22	11.19	10.88	15.56
CV (%)	55	30	40	30	23	33
Minimum	2.0	21.0	12.0	13.0	34.0	36.0
Maximum	60.0	57.0	46.0	71.0	72.0	58.0
N	26	18	18	91	10	2
CI	5.89	4.86	5.18	2.30	6.74	21.56
p-value	- x -	0.309	1.000	0.010	< 0.001	0.246

SCA: Spinocerebellar ataxia; SCA7: SCA type 7; SD: Standard deviation; CV: Coefficient of variation; N: Number; CI: Confidence interval.

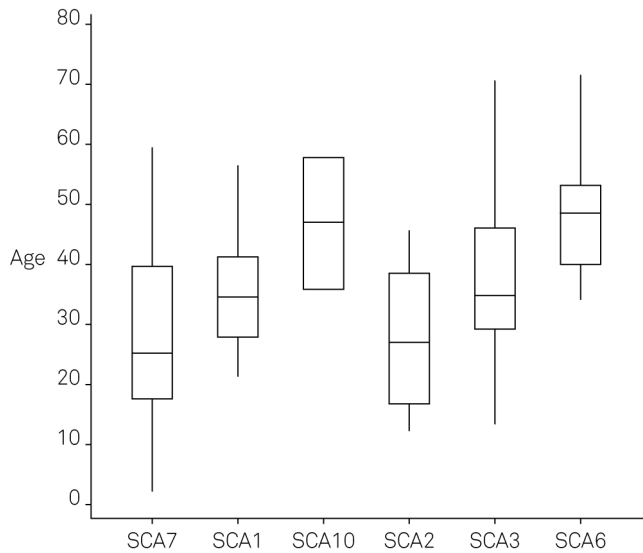


Figure. Box-Plot comparing spinocerebellar ataxia type 7 (SCA7) with each spinocerebellar ataxia (SCA) regarding age of onset of ataxia symptom.

manifesting later than transmitting parent. Of note, one patient had atypical neurological manifestation, characterized by chorea and dystonia during disease progression.

DISCUSSION

This article highlights the wide clinical variability in SCA7 patients, considering the first neurological manifestation age at onset and genetic anticipation.

SCA7 accounts for approximately 2 to 5 percent of all SCA and has a variable clinical expression, particularly depending on age at onset and CAG repeat⁷. Thus, the higher the number of repetitions, the more severe the disease, and the earlier the onset of symptoms⁷. Extremely long CAG repeats (> 150) are associated with very early onset ataxia¹². This fact has two major concerns: firstly, it

is a clinical marker for the dramatic genetic anticipation in SCA7; secondly, these patients might be confused as having autosomal recessive ataxias.

Since genetic anticipation and marked instability of the repeated sequence is a hallmark in SCA7 we demonstrated this phenomenon in patients whose age at onset is very early, as we described in the 4 patients with onset of symptoms before the age of 10-year-old. Moreover, this instability of the repeated sequences is also seen in some parents since they developed the disease after the symptoms had already flourished in their children, as observed in two patients of our sample. Another important finding is the predominance of marked anticipation when the inheritance is from the mother. This pattern was also seen in previously described SCA7 families. One possible explanation is that mothers appear to be more consistent in passing on expanded alleles and thus maintaining disease within kindreds¹⁴.

Several potential mechanisms for the molecular pathogenesis of poly-Q expanded ataxin-7 in SCA7 patients have been suggested, and may include: alteration of endogenous ataxin-7 function, abnormal processing and stability of polyQ ataxin-7, and alteration of transcriptional regulation via interaction of polyQ-expanded ataxin-7 with other transcriptional regulators. The CAG repeat sequence is particularly unstable and *de novo* mutations can occur during paternal transmissions of intermediate size alleles. This can explain why SCA7 did not result in extinction, in spite of the anticipation. In general, some review articles differentiate SCA7 patients in 4 different groups: (1) asymptomatic young carriers (38 to 43 CAG repeats); (2) late onset ataxia, and mildly symptomatic (38 to 41 repeats); (3) patients with the typical clinical spectrum, and age onset during adolescence (around 55 repeats); and (4) children with very early onset and rapid course (over 55 repeats)^{15,16,17}. In our sample, we had no asymptomatic young carriers; there were 3 patients with late onset ataxia and mildly symptomatic (39-44 CAG repeats); 19 patients with the typical phenotype (41-53 CAG repeats); 4 children with very

Table 2. Intra-group analysis in SCA7 patients considering demographic and clinical features, age at onset of the ataxia and visual symptoms. CAG repeat length and severity.

Variable	Age of symptoms onset earlier than the transmitting parent (SCA7 patients n = 22)	Age of symptoms onset later than the transmitting parent (SCA7 patients n = 4)	p-value
Age (mean ± SD)	31 ± 14.9	54.8 ± 3.4	0.006
Disease duration / ataxia (mean ± SD)	6.8 ± 4	9 ± 4.4	0.401
Duration of visual symptoms (mean ± SD)	9.3 ± 5.8	19 ± 15	0.241
Age of onset of ataxia (mean ± SD)	24.1 ± 13.1	44.7 ± 6	0.024
Age of onset of visual impairment (mean ± SD)	21.6 ± 13.5	34.7 ± 17.6	0.241
CAG repeat length (mean ± SD)	51.4 ± 7.4	41.3 ± 2.5	0.014
ICARS (mean ± SD)	52.7 ± 20.7	46.3 ± 14.6	0.596
SARA (mean ± SD)	19.2 ± 6.9	19 ± 17	0.958

SCA7: Spinocerebellar ataxia type 7; SCA: Spinocerebellar ataxia; SD: Standard deviation; ICARS: International Cooperative Ataxia Rating Scale; SARA: Scale for the Assessment and Rating of Ataxia.

early onset (before 10-year-old) and rapid course (more than 56 CAG repeats).

In conclusion, our study demonstrates the genetic anticipation phenomenon that occurs in SCA7 families. This fact results in two interesting observations: firstly, patients with SCA7 may present a very early onset phenotype (childhood onset); and secondly, occasionally the parents may have the onset of symptoms after their children. Patients with very early onset ataxia (before 10-year-old) in the context of a

remarkable family history (SCA). must be considered and tested for SCA7.

Acknowledgments

We thank Dr. Laura B. Jardim, Dr. Maria Luiza Saraiva-Pereira and Dr. Raphael Castilhos for having provided genetic testing for our patients.

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