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## Spinocerebellar Ataxia Type 10: Frequency of epilepsy in a large sample of Brazilian patients

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### Abstract

Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant disorder caused by an ATTCT repeat intronic expansion in the SCA10 gene. SCA 10 has been reported in Mexican, Brazilian, Argentinean and Venezuelan families. Its phenotype is overall characterized by cerebellar ataxia and epilepsy. Interestingly, Brazilian patients reported so far showed pure cerebellar ataxia, without epilepsy. Here, authors provide a systematic analysis of the presence, frequency and electroencephalographic presentation of epilepsy among 80 SCA10 patients from 10 Brazilian

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families. Overall, the frequency of epilepsy was considered rare, been found in 3.75 % of the cases while this finding in populations from other geographic areas reaches 60% of SCA10 cases.

## Keywords

Spinocerebellar ataxia type 10; SCA; autosomal dominant cerebellar ataxia; epilepsy

Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant disorder caused by a large expansion of a pentanucleotide (ATTCT) repeat in the intron 9 of the SCA10 gene on chromosome 22.<sup>1-5</sup> SCA10 is the only neurodegenerative disease caused by an expansion of a pentanucleotide repeat. Pathogenic alleles range from 800 to 4500 ATTCTs (normal 10 to 29).<sup>1,3</sup> SCA10 has previously been reported in Mexican families, in which the disease presented with a unique combination of pure cerebellar ataxia, epilepsy and, at times, polyneuropathy, pyramidal signs and cognitive dysfunction.<sup>1-5</sup> In 2004 we described the clinical phenotype of 5 Brazilian families with SCA10 presenting with pure cerebellar ataxia but no associated epilepsy.<sup>6</sup>

The objective of our study is to analyze the frequency and characteristics of epilepsy in a large sample of Brazilian patients with SCA10.

## Methods

We studied 80 patients from 10 unrelated families with SCA10, selected out of 180 Brazilian genetically proven SCA families followed at the Hospital de Clínicas, Federal University of Paraná in Curitiba, Brazil, from 1990 to 2009. This cohort includes all cases of SCA 10 diagnosed so far in our service. Signed informed consent was obtained based on a protocol approved by the local Ethics Committee. Five of these ten families have already been published by the authors elsewhere.<sup>6</sup> All patients were evaluated by 3 neurologists (HT, WOA, RPM) and a medical geneticist (SR). History, physical examination, and routine laboratory tests, including complete blood count, blood urea nitrogen, creatinine, electrolytes, glucose, liver and thyroid function tests, and VRDL, were performed. The diagnosis of epilepsy was ascertained via clinical history. Detailed family history of each patient was obtained and the information was double-checked with close relatives. The following studies were also performed in all patients: brain CT and MRI, electroencephalography (EEG) and routine CSF analysis. Molecular analysis of the ATTCT repeat expansion in the SCA10 gene was performed by polymerase chain reaction (PCR) amplification using primers attct-L (5'-AGAAAACAGATGGCAGAATGA-3') and attct-R (5' GCCTGGGCAACATAGAGAGA-3'), as described previously. Patient DNA samples that showed a single normal SCA10 allele by PCR underwent Southern blot analysis to assess large expansions.

## Results

From the total 80 patients examined, 40 (50%) were male with mean age of onset of 35.5 years, and mean disease duration of 15.3 years. Among the 10 families, number of affected members studied varied from 1 (ref.<sup>7</sup>) to 21 subjects (mean 8 per family). All patients presented with cerebellar syndrome (predominantly gait ataxia, with dysarthria and nystagmus). Six (7.5%) patients had mild lower limbs hyperreflexia with spasticity in three. Three (3.75 %) of the 80 patients had a history compatible with seizures, including, generalized tonic-clonic seizures in two cases and a combination of myoclonic, complex partial and generalized tonic-clonic seizures, with occasional status epilepticus in the third patient. The later case has been previously published as a 28-year-old woman with

progressive cerebellar ataxia starting at childhood, followed by seizures/epilepsy (at age 23 y/o) and progressive cognitive dysfunction (at age 24 y/o), and definite dementia (at age 27 y/o).<sup>7</sup> Both cases with tonic-clonic seizures belonged to the same family. This family is the largest of our cohort with 21 affected members studied so far. Molecular genetic testing of this patient showed an expanded allele of 850 ATTCT repeats. The other 2 patients with SCA 10 and epilepsy had expanded alleles with 1250 (35-year-old female patient) and 1500 repeats (55-year-old male patient).

Brain MRI of all index cases (n: 10) showed cerebellar atrophy. Brainstem atrophy was found in 3 cases and brain atrophy in 1 case. Interictal EEG of these three cases was abnormal in only one patient, showing diffuse disorganization but no clear cut epileptiform activity (patient published previously).<sup>7</sup> Patients with SCA10 with epilepsy did not differ from molecular and demographic standpoints in regards to those with pure cerebellar ataxia.

The comparison between Brazilian, Mexican (published by Rasmussen *et al.*<sup>4</sup>), Argentinean and Venezuelan patients, with SCA10 is showed in the table 1.

## Discussion

Spinocerebellar ataxia type 10 (SCA10) is an autosomal dominant neurodegenerative disease initially described only in Mexican families.<sup>1-6</sup> In 2002, Matsuura *et al.*<sup>8</sup> studied the presence of SCA in several non-Mexican populations, including White American, French-Canadian, Italian, Japanese, and Spanish patients, in whom no pathogenic ATTCT expansion repeat was detected. Later, Teive *et al.*<sup>6</sup> reported on 28 SCA 10 patients from five new Brazilian families with a new phenotype: pure cerebellar ataxia, without epilepsy. This study also showed that SCA10 is the second most common autosomal dominant cerebellar ataxia (ADCA) in Brazil (after SCA type 3), as is had already been shown for the Mexican population where SCA type 2 is the most common form. In both countries all SCA10 families reported Amerindian ancestry.<sup>4,6,7,9</sup> Two additional reports on non-Brazilian South American populations diagnosed with SCA 10 were published more recently. Gatto *et al.*<sup>10</sup> reported on two SCA 10 Argentinean patients presenting with cerebellar ataxia and epilepsy, associated with additional motor signs (dystonia in one case and parkinsonism on the other). Gallardo and Soto<sup>11</sup> described a patient from Venezuela, also genetically confirmed with SCA 10, in whom cerebellar ataxia and cognitive dysfunction coexist with epilepsy. Almeida *et al.*<sup>12</sup> studied the ancestral origin of the ATTCT repeat expansion in SCA10 concluding that there may be a common ancestral for SCA10 in Latin America, probably with Amerindian origin, who later on spread into the mixed populations of Mexico and Brazil.

Here, we report a large series of Brazilian patients with the SCA10 mutation, showing that epilepsy, one of the particular aspects of this disorder in Mexico, Argentina and Venezuela, is very uncommon, leaving the presentation of a pure cerebellar ataxia. The incidence of epilepsy in developed countries is reportedly between 0.04 and 0.07 % / year. In resource-poor countries, these figures are higher, around 0.12 % / year with prevalence rates between 0.6 and 1 %<sup>13</sup>. These figures were recently confirmed in a descriptive study of epilepsy epidemiology, with the caveat that regional environmental exposures and socioeconomic status may have biased the statistics.<sup>14</sup> Specifically, data regarding to the epidemiology of epilepsy in Brazil is somewhat scattered. A recent project by Li *et al.*<sup>15</sup>, part of a WHO/ILAE/IBE Global Campaign, disclosed a prevalence of 0.92 %. Thus, the 3.75% rate of epilepsy in our sample appears to rest above the expected frequency in the general population but significantly below the 60 % reported in Mexican families with SCA 10.

These data demonstrated that the phenotypic expression of the SCA10 mutation in Brazilian families, with predominantly pure cerebellar ataxia, is rather different from Mexican, as well as from Argentinean and Venezuelan cases, where cerebellar ataxia and epilepsy represent the most common phenotype (up to 60 % in the Mexican patients). Our 3 patients with epilepsy presented with generalized tonic-clonic seizures in 2 cases, and in only one case, previously published, we found myoclonic seizures, complex partial seizures and generalized tonic-clonic seizures. This patient had a progressive cerebellar ataxia, with epilepsy and dementia. Brain MRI of these cases showed predominantly cerebellar atrophy and the EEG tracings did not reveal specific abnormalities.

Based in our cohort, the differing phenotype of Brazilian and Mexican patients cannot be explained based on the ATTCT repeat expansion size, mostly because the repeat size of these two SCA 10 populations overlapped. Of importance, in the Mexican SCA 10 patients with epilepsy there was a wide range of the repeat expansion sizes, suggesting that this molecular variable is probably not independently related with epilepsy.<sup>6</sup> Other alternative explanations, such as somatic and germline instability of the ATTCT repeat in SCA 10 and the effect of interruptions in the expanded ATTCT repeats, may contribute to this phenotypic variation and should be studied in future investigations.<sup>16-18</sup>

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**Table 1**

Clinical and Genetic aspects of Brazilian, Mexican, Argentinian and Venezuelan patients with SCA 10.

	<b>Brazilian patients</b>	<b>Mexican patients</b>	<b>Argentinean patients</b>	<b>Venezuelan patients</b>
Number of patients	80	19	5	5
Age of onset (years)	35.5 (22-46)	26.7 (14-44)	35	14 (case report)
Number of ATTCT repeats	1820 (20)	2838	1100	4400
Correlation between size of ATTCT repeats and age of onset	Inverse correlation	Inverse correlation	-	-
Cerebellar ataxia	100 %	100 %	100%	100%
Pyramidal signs	6 (mild hyperreflexia), 3(mild spasticity)	6 ("soft" pyramidal signs),2 (pyramidal signs)	2	-
Epilepsy	3.75 %	72.2 %	100%	80%
Peripheral Neuropathy	0 %	66 %	-	-
Ethnic origin (by history)	Indian ancestry 75 %	Indian ancestry 100%	Mixed Spanish and Amerindian	Unknown