

Spinocerebellar ataxia type 3: subphenotypes in a cohort of brazilian patients

Ataxia espinocerebelar do tipo 3: subfenótipos em uma coorte de pacientes brasileiros

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ABSTRACT

Spinocerebellar ataxia type 3 (SCA3) involves cerebellar, pyramidal, extrapyramidal, motor neuron and oculomotor systems with strong phenotypic heterogeneity, that lead us to classify the disorder into different clinical subtypes according to the predominantly affected motor systems. **Method:** The series comprises 167 SCA3 patients belonging to 68 pedigrees, studied from 1989-2013. These patients were categorized into seven different subphenotypes. **Results:** SCA3 cases were clustered according to the predominant clinical features. Three most common forms were subphenotype 2, characterized by ataxia and pyramidal symptom was observed in 67.5%, subphenotype 3 with ataxia and peripheral signs in 13.3%, and subphenotype 6 with pure cerebellar syndrome in 7.2%. **Conclusion:** Our study was the first to systematically classify SCA3 into seven subphenotypes. This classification may be particularly useful for determination of a more specific and direct phenotype/genotype correlation in future studies.

Keywords: Machado-Joseph disease, subphenotypes, spinocerebellar ataxia type 3.

RESUMO

A ataxia espinocerebelar do tipo 3 (AEC3) envolve os sistemas cerebelar, piramidal, extrapiramidal, do neurônio motor e oculomotor, com uma grande heterogeneidade fenotípica, o que nos levou a classificar essa desordem em diferentes subtipos clínicos de acordo com o sistema predominantemente afetado. **Método:** Nossa série compreende 167 pacientes com AEC3, pertencentes a 68 famílias, avaliados de 1989 a 2013. Esses pacientes foram classificados em 7 diferentes subtipos. **Resultados:** Os pacientes com AEC3 foram agrupados de acordo com as características clínicas predominantes. As três formas mais comuns foram o subfenótipo 2, caracterizado por ataxia e sintomas piramidais, observado em 67,5% dos pacientes, subfenótipo 3 com ataxia e sinais periféricos, em 13,3%, e subfenótipo 6 com síndrome cerebelar pura, em 7,2%. **Conclusão:** Nosso estudo foi o primeiro a classificar sistematicamente AEC3 em sete subtipos. Esta classificação pode ser particularmente útil para correlacionar fenótipo/genótipo com mais especificidade em futuros estudos.

Palavras-chave: doença de Machado-Joseph, subfenótipos, ataxia espinocerebelar tipo 3.

Machado-Joseph disease (MJD), also known as spinocerebellar ataxia type 3 (SCA3), is the most frequent form among the autosomal dominant cerebellar ataxias worldwide, particularly in Portugal, Brazil, Japan and China, with some expected geographic variations of prevalence^{1,2,3,4,5}. As other dominantly inherited ataxias, SCA3 shows remarkable clinical heterogeneity, reflecting the underlying genetic defect: an unstable CAG trinucleotide repeat that varies in size among affected patients¹.

This wide range of clinical manifestations include cerebellar ataxia, affecting gait, limb movements, speech articulation and swallowing; a pyramidal syndrome, with brisk deep tendon reflexes, Babinski sign, and spasticity;

supranuclear, progressive external ophthalmoplegia (PEO), with early limitation on upward gaze and convergence; extrapyramidal signs, including dystonia, rigidity and/or bradykinesia; lower motor neuron disease, with fasciculations and amyotrophy; sensation loss; eyelid retraction; weight loss; and sleep disorders⁶.

The striking clinical heterogeneity in SCA3 has been described since its initial description. In fact, in the 70's, the observation of three families of Azorean ancestry (Machado, Thomas and Joseph), living in the United States of America, by three distinct groups of researchers, led to the initial description of three apparently independent diseases^{7,8,9}. The subsequent identification of several

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Portuguese families living both in the Azores Islands and in Portugal mainland, including subjects presenting the three phenotypes described, led to the unification of the disease as a single genetic entity, with variable phenotypic expression¹⁰. However, three typical phenotypes were proposed by Coutinho and Andrade¹⁰ in 1978 and are widely accepted: (i) Type 1 patients (type Joseph) have earlier onset and more severe clinical course, with severe dystonia and pyramidal signs, PEO, appendicular and gait ataxia; (ii) In type 2 (type Thomas) patients present with intermediate age of onset and have predominantly cerebellar and pyramidal deficits with PEO; (iii) Patients with type 3 (type Machado) present later onset, less severe disease, with peripheral signs, gait and limb ataxia with the variable presence of PEO and pyramidal signs.

In addition to these well-known phenotypes, other variants have been proposed. Some authors consider as type 4, a presentation with the parkinsonian triad (resting tremor, bradykinesia and rigidity), almost indistinguishable from idiopathic L-dopa-responsive Parkinson's disease. These patients' symptoms also include mild cerebellar signs and distal motor sensory neuropathy or amyotrophy^{11,12,13,14}. Also, Sakai reported two Japanese siblings which originally presented spastic paraparesis¹⁵. Subsequently, Kaneko et al.¹⁶ and Teive et al.¹⁷ found similar families, suggesting this to be a fifth subtype. In 1996, Ishikawa et al.¹⁸ described a patient presenting with pure cerebellar ataxia (type 6). Finally, our own group has observed an additional subphenotype 7, with a mixed form that includes ataxia and levodopa responsive parkinsonism (Table 1). This subphenotype, different from phenotype 4, present with a very mild ataxia, marked pyramidal signs, with important spasticity, and predominantly rigid-akinetic parkinsonism. These patients do not have tremor neither distal motor sensory neuropathy nor amyotrophy.

Other possible presentations include a stiff person syndrome described by Berciano et al.¹⁹, motor neuron disease described by Pinto and De Carvalho²⁰, and the occurrence of akathisia, described by Pedroso et al.²¹.

The main purpose of this study was to validate these subphenotypes and further determine their clinical characteristics and frequency in a cohort of Brazilian patients.

METHOD

All patients were evaluated at the Movement Disorders Unit of the Federal University of Paraná, from 1989 to 2013. Included patients were assessed using a standardized protocol, including demographic, clinical and paraclinical (blood tests, neurophysiological and neuroimaging) data, and molecular genetic testing for SCAs types 1, 2, 3, 6, 7, 8, 10, 12, 14, 17 and DRPLA. After a detailed analysis of the clinical features of the patients with a confirmed diagnosis of SCA3, the senior author classified them according to different subphenotypes, as previously described (Table 1).

Signed informed consents were obtained following a protocol approved by the Institutional Ethics Committee of the Federal University of Paraná.

RESULTS

From a total of 373 patients (167 families), 273 (73.4%) presented a specific molecular diagnosis. SCA3 was found in 68 families, a total of 167 patients (61.2%). Other subtypes detected included SCA10 in 24.1% of patients, SCA2 in 7.3%, SCA1 in 3.7%, SCA7 in 2.6%, and SCA6 in 1.1% of SCA patients.

From a demographic standpoint, 92 (55%) of the SCA3 patients were male, with a mean age of 44.6±12.1 years, mean age of onset of 35.6±9.2 years, and mean disease duration of 9±7.2 years.

Out of the whole sample of 167 patients with SCA3, 10 (6%) were classified with subphenotype 1, 111 (66.4%) with subphenotype 2, 22 (13.2%) with subphenotype 3, 4 (2.4%) with subphenotype 4, 1 (0.6%) with subphenotype 5, subtype 6 in 12 (7.2%) and subphenotype 7 in 5 (3%) of cases. Other presentations, including stiff person-like syndrome and motor neuron disease, were found in 1.2% of the cases, as shown in Table 2.

Clinical and demographic data according to subphenotype are described in Table 3. We found no significant difference between the subphenotype and CAG repeat expansion (expanded alleles varies from 56 to 70 CAG repeats).

Table 1. Clinical characteristics of spinocerebellar ataxia type 3 subphenotypes.

	Phenotype 1	Phenotype 2	Phenotype 3	Phenotype 4	Phenotype 5	Phenotype 6	Phenotype 7
Cerebellar ataxia	++	++	++	+/-	-/+	+++	++
Extrapyramidal signs							
Dystonia	+++						
Parkinsonism	++			+++			++
Pyramidal syndrome	+++	++	-/+				++
PEO	++	+++	-/+				+
Peripheral signs			+++	+			
Spastic paraparesia					+++		

PEO: Progressive external ophthalmoplegia.

Table 2. Spinocerebellar ataxia type 3: subphenotypes frequency.

Subphenotypes	Features	n (%)
Subphenotype 1	Dystonia/parkinsonism/ataxia	10 (6.0)
Subphenotype 2	Ataxia/pyramidal signs	111 (66.4)
Subphenotype 3	Ataxia/peripheral signs	22 (13.2)
Subphenotype 4	Parkinsonism	4 (2.4)
Subphenotype 5	Spastic paraparesis	1 (0.6)
Subphenotype 6	Pure cerebellar syndrome	12 (7.2)
Subphenotype 7	Mixed type (ataxia, pyramidal signs, and levodopa responsive parkinsonism)	5 (3.0)
Others	Stiff-Person like, ALS-like	2 (1.2)

ALS: Amyotrophic lateral sclerosis.

DISCUSSION

SCA3 is an autosomal dominant, multisystem, neurodegenerative disorder that presents with significant phenotypic variability, even within the same family^{15,22}. In the series presented here, the subphenotype most commonly found was type 2, which is the classic form described in the literature²³. Other classic phenotypes described by Coutinho and Andrade²³ were types 1 and 3, found in a small percentage of patients.

There are only a few reports of a Parkinson's disease-like phenotype in SCA3 patients^{11,12,13,14}. The subphenotype 4 is characterized by parkinsonism variably combined with ataxia and peripheral neuropathy. This form of SCA3 has been previously reported to occur in African American families, suggesting an ancestry of this phenotype^{12,13}. Although these parkinsonism phenotypes are rare in those of European descent, none patient of our research was descending African.

The mixed type, subphenotype 7, is characterized by very mild ataxia, pyramidal signs with severe spasticity, and rigid-akinetic parkinsonism. We emphasize the fact that levodopa usually is an effective form of treatment in this group of SCA3 patients¹⁴. In addition, other described phenotypes, such as type 5, were rare in our sample. Sakai and Kawakami first reported two siblings, whose parents suffered from Parkinson's disease and SCA3 respectively, which presented spastic paraplegia at the very onset. So far, a few subtype 5 families have been reported^{15,16,17,24,25}. Wang et al.²⁵ investigated the incidence of mutation in the SCA3 gene among patients clinically diagnosed as spastic paraplegia. They found

expanded CAG repeats that ranged from 64 to 81 in 13% of cases.

Ishikawa¹⁸ described subphenotype 6 in a patient with late onset pure cerebellar ataxia. The patient reported had a son with gait disturbance, mild ophthalmoparesis, and mild spasticity with brisk tendon reflexes. Sixty-six repeats were found in the patient and 73 in the son, suggesting that patients with relatively small repeat numbers would show late-onset pure cerebellar ataxia.

Stiff person-like syndrome and neuron motor disease were single cases, and akathisia variant was not found in our series.

Although the classical be the most common form, just because the overlap of the clinical manifestation between SCA3 and other disease, like spastic paraplegia, Parkinson disease and motor amyotrophic lateral sclerosis, some patients are misdiagnosed, and then, we must know the other subphenotypes to make the correct diagnosis.

It is possible that during the course of the disease new symptoms may appear and change the phenotype of the patient. These can be a limitation of our cross-sectional study, and, thus, a prospective research should be done to clarify this question.

Another point to be evaluated in future studies concerning the severity of ataxia related to subphenotype, raising the possibility that different forms of disease could have more severe symptoms.

Our study was the first to systematically classify SCA3 into seven subphenotypes. This classification may be particularly useful for the determination of a more specific and direct phenotype/genotype correlation in future studies.

Table 3. Clinical and demographic data according to subphenotype.

	Type 1	Type 2	Type 3	Type 4	Type 5	Type 6	Type 7
Mean age of onset±SD	27.4±9.1	34.9±7.1	44.1±13.0	36.2±8.2	41	33±11.0	32.2±7.2
Mean disease duration±SD	7.3±5.9	9.1±7.5	11.1±6.4	13±6.3	3	5±6.1	85.9
Mean triplet expansion±SD	76.4±1.5	70.3±5.0	67.3±6.9	72.3±4.5	66	72.3±3.9	73.2±3.8

SD: standard deviation.

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