Clinical relevance of “bulging eyes” for the differential diagnosis of spinocerebellar ataxias

Relevância clínica do “bulging eyes” para o diagnóstico diferencial das ataxias espinocerebelares

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Spinocerebellar ataxias (SCA) are autosomal dominant inherited ataxias, which constitute a heterogeneous group of typically late-onset, progressive, and often fatal neurodegenerative disorders. Globally, SCA are considered rare disorders, with prevalence estimates varying from 1 to 5 cases per 100,000 individuals1. Machado-Joseph disease, also known as spinocerebellar ataxia type 3 (SCA3), is currently considered the most common form of SCA worldwide. Among SCA, the relative frequency of SCA3 in Brazil is about 69–92%2,3.

SCA3 is a multisystem neurodegenerative disorder involving predominantly the cerebellar, pyramidal, extrapyramidal, motor neuron and oculomotor systems. Minor, but more specific features such as external progressive ophthalmoplegia (EPO), dystonia, intention fasciculation-like movements of facial and lingual muscles, as well as bulging eyes (BE), may also be of major importance for the clinical differential diagnosis of SCA3.

The main purpose of this study was to investigate the relevance of the finding of BE in a large Brazilian cohort of spinocerebellar ataxias (SCA), to assess its importance in clinical differential diagnosis among SCA.

Methods

There were studied 369 patients from 168 families with SCA extracted from a large Brazilian cohort. Inclusion criteria

Study carried out at Hospital de Clínicas, Universidade Federal do Paraná (UFPR), Curitiba PR, Brazil.

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were a progressive clinical phenotype in which ataxia was the prominent symptom and a positive familial history compatible with autosomal dominant inheritance. Patients with ataxia secondary to alcohol abuse, inflammatory, neoplastic, paraneoplastic, vascular, or well-defined metabolic diseases were excluded from this study. All patients were assessed with neurological examination and molecular genetic testing for SCA types 1, 2, 3, 6, 7, 10, 12, 14, 17 and dentatorubral-pallidoluysian atrophy (DRPLA).

BE was characterized by the presence of eyelid retraction or eyelid lag according to predefined literature definitions and included in clinical criteria of Machado-Joseph disease by Coutinho et al (Figure).

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

RESULTS

A mutation was identified in 74.3% of the patients, with SCA3 being the most frequent (45.3%). SCA10 represented the second most common (18.4%), followed by SCA2 (5.4%), SCA1 (2.4%), SCA7 (1.6%), and SCA6 (0.8%). The remaining 25.7% of patients were left undiagnosed genetically.

Among the affected patients examined, 53.7% were male. Age at onset ranged from 6 to 75 years with a mean of 34.5±10.0 years, and time from disease onset was 9.3±7.4 years (variance 1–37 years).

Table 1 shows a brief summary of clinical data of the SCA type 1, 2, 3, 6, 7, 10 and the overall group of SCA. In comparison with other SCA, those patients with SCA3 presented more frequently with eyelid retraction. BE was detected in 123 patients with SCA (33.3%), namely 109 (65.2%) of the 167 SCA3 patients and in 5 (4.7%) of the others SCA patients (1 SCA10 patient, 2 SCA1 patients and 2 SCA2 patients) (Table 2). BE was significantly more frequent among patients with SCA3 than among those with other forms of genetically defined SCA (p<0.0001, Yates correction, OR 37.96 95%CI 14.6–98.4). There was no correlation between the presence of BE and the repeat length in the different genes. In the group of 96 SCAs patients without detected mutation BE was found in 9 patients (9.37%).

DISCUSSION

SCA3 is characterized by a high degree of pleomorphism, not only in the variability in the age of onset and in neurological signs but also in the resulting loss of functionality. In general, the initial symptoms occur during adulthood, with a mean age of onset of 32±12 years among Brazilian patients. However, the range of age of onset is wide in other series, spanning from 5 to 73 years in Portuguese patients.

Since the classic description of SCA3 by Coutinho and Andrade in 1978, followed by other studies from the same group, most investigators have emphasized the presence of a characteristic phenotype that includes ophthalmoplegia, BE, facial fasciculations, pyramidal signs, peripheral neuropathy, as well as dystonia in younger patients. More recently, the observation of variant phenotypes in SCA3 led to the description of sub-phenotypes: subtype I, with predominant extrapyramidal signs and dystonia; subtype II with cerebellar ataxia (CA) and pyramidal tract signs; subtype III (with CA and signs of peripheral neuropathy); subtype IV with parkinsonism; and subtype V resembling spastic paraplegia. BE due to eyelids retraction, dystonia, and fasciculations are minor but rather characteristic features of SCA3. In the classical study of Lima e Coutinho from Portugal, BE was found in 34.8% of the patients and was considered a very suggestive sign of SCA3.

BE due to retraction of the eyelids, with consequent widening of the palpebral fissures, was described by James Collier in 1937, as “tucked lids”, and is worldwide known as Collier’s sign. In this seminal paper, Collier defined that retraction of the eyelids occurs due to a lesions of the upper brainstem (midbrain), in the region of the posterior comissure, associated with ophtalmoplegia, and frequently found in degenerative diseases.

In this study, BE was present in 33.3% of patients, however, it was particularly more common among SCA3 patients, occurring in almost two thirds of cases. On the other hand, this ocular finding was detected in only 13.2% of cases with other SCA (4.7% of others genetically confirmed SCA and 9.3% of SCA without genetic diagnosis). Intriguingly, the study by Schöls et al. describing German patients, did not find the typical signs described in Portuguese SCA 3 cases such as BE, dystonia, and rigidity. These findings were observed in only one out of 42 German patients. This observation is in line with the viewpoint shared by Jacobi et al.
among other groups, who state that there is a significant overlapping among different SCA, impeding purely clinical based diagnoses11.

Stevanin, Dürr and Brice12 suggested that BE is not common among non-Portuguese Western European SCA3 patients, and might, therefore, be related to ethnic background. Finally, other authors have attempted to describe oculomotor phenotypes suggestive of several forms of SCA13; however these finding have no significant impact in daily clinical practice.

The phenotypic difference among Brazilian and Portuguese patients with SCA3 and patients from others countries (particularly European countries, such as, Germany and France), regarding the presence of BE, could be explained by many reasons, including the role of others regulatory genes, as well as environment factors. However, if one compare the frequency of BE in Portuguese SCA3 patients (33.4%) with Brazilian SCA3 patients in the present series (65.2%), it is noticeable that the frequency of BE in our series is very significant.

In this large Brazilian cohort of SCA patients BE was detected in the majority of patients with SCA3 (65.2%) and could be used as a clinical tool for the differential diagnosis of SCA.

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**Table 1. Demographics of spinocerebellar ataxias patients.**

| Clinical Data       | SCA1 | SCA2 | SCA3 | SCA6 | SCA7 | SCA10 |
|---------------------|------|------|------|------|------|-------|
| Patients number     | 9    | 20   | 167  | 3    | 6    | 68    |
| Gender              |      |      |      |      |      |       |
| Male                | 6    | 13   | 92   | 1    | 3    | 32    |
| Female              | 3    | 7    | 75   | 2    | 3    | 36    |
| Age of onset (years/mean) | 37.2 | 28.5 | 35.6 | 42.7 | 31.0 | 34.0 |
| Disease duration (years/mean) | 5.89 | 9.20 | 9.02 | 12.67| 10.67| 10.68|

SCA: spinocerebellar ataxia.

**Table 2. Spinocerebellar ataxias: frequency of bulging eyes.**

| SCA type                  | Total patients with SCA | Number of patients with BE | % of BE |
|---------------------------|-------------------------|----------------------------|---------|
| SCA3                      | 167                     | 109                        | 65.2    |
| Others SC (1,2,6,7,10)    | 106                     | 5                          | 4.7     |
| SCA (without mutation)    | 96                      | 9                          | 9.4     |

SCA: spinocerebellar ataxia; BE: bulging eyes.