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LETTER TO THE EDITOR

Depressive Mood is Associated with Ataxic and Non-Ataxic Neurological Dysfunction in SCA3 Patients

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We read with interest the article recently published in *Cerebellum* by Klinke et al., entitled "Neuropsychological features of patients with spinocerebellar ataxia (SCA) types 1, 2, 3, and 6," particularly because it pertains to the depressive mood scores obtained in those patients [1]. SCAs are a group of autosomal dominant ataxic disorders affecting mainly the cerebellum and its afferent and efferent connections; however, in most SCAs the consecutive degenerative process also involves extracerebellar structures [2].

A recent survey of subjective health status performed in 526 SCA patients from the European Integrated Project on Spinocerebellar Ataxias (EUROSCA) clinical group, found that 46% of those patients reported depression/anxiety problems, which was one of the three independent predictors of subjective health status together with ataxia severity and extent of noncerebellar involvement [3]. We previously reported that SCA3 symptomatic patients have higher depressive mood scores on the Beck Depression Inventory (BDI) than controls (caregivers), whereas their children at risk have BDI scores lower than the same control group. Depressive mood scores on the BDI correlated with the neurological disability measured by the Barthel Index of Physical Incapacitation in our study [4], and correlated with the dominant motor hand dysfunction in the study of Klinke et al. [1].

In order to further evaluate depressive symptoms in SCA3 patients and their relationship with the recently obtained ataxia scores, we performed a case–control study in 49 molecularly confirmed SCA3 patients from the neurogenetics clinic of Hospital de Clínicas de Porto Alegre (HCPA), and 41 healthy, nonrelated individuals with similar age, gender, and environmental characteristics—such as spouses or neighbors of the affected individuals (mainly caregivers)—as the control group. The *ATXN3* expanded regions were analyzed as previously described [5].

The BDI, in its Brazilian version [6], was applied to quantify the depressive symptoms of subjects. BDI is usually interpreted as follows: 0–10 (absence or subtle depression), 11–18 (mild depression), 19–29 (moderate depression), and 30–63 (severe depression).

Two clinical ataxia scales were applied: the Scale for the Assessment and Rating of Ataxia (SARA) [7], which evaluates ataxic signals, and the Neurological Examination Score for Spinocerebellar Ataxia (NESSCA) [8], which is a global neurological evaluation encompassing ataxic and non-ataxic signals. Both scores vary from 0–40 points, increasing with disease severity. Data on disease duration and age of onset were provided by patients and their relatives.

For detailed patient characteristics, see Table 1. SCA3 patients presented higher depressive scores on BDI ($p=$

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Table 1 Demographics of the enrolled individuals

	Controls Mean (SD)	SCA3 Patients Mean (SD)	*p*
N	41	49	NA
Age (years)	45.6 (12.8)	44.5(11.2)	0.689
Gender (M/F)	16/25	23/26	0.450
BDI	10.5 (9)	15.9 (10.9)	0.012*
Disease duration (years)		9.96 (6.4)	NA
Age at onset (years)		34.6 (10.3)	NA
CAG(*n*)		73.3 (3)	NA
NESSCA		17.5 (6)	NA
SARA		14.5 (7.5)	NA

BDI, Beck Depression Inventory; SARA, Scale for the Assessment and Rating of Ataxia; NA, not applicable, NESSCA, Neurological Examination Score for Spinocerebellar Ataxia

0.012) when compared to controls (Fig. 1a). Considering the severity of depressive symptoms, 61% of controls versus 36.7% of SCA3 patients had absence of or subtle depression, 17% versus 28.5% had mild, and 22% versus 34.6% had moderate or severe scores on BDI (Fig. 1b). BDI correlated moderately with SARA (R=0.359, p=0.01, Fig 1c) and NESSCA (R=0.412, p=0.003, Fig. 1d). When dividing NESSCA into two subscores, the first related to ataxic signals (maximum of 16 points) and the second to non-ataxic signals (maximum of 24 points), both scores correlated significantly with BDI (R=0.411, p=0.003; R=0.348 p=0.01, respectively). BDI was also correlated with disease duration, although it did not achieve statistical significance (R=0.273 p=0.057). BDI was not associated with other clinical or molecular parameters of SCA3 (data not shown).

We also randomly performed magnetic resonance imaging (MRI) (1.5T system) in 30 (16 females) of these SCA3 patients—whose demographic characteristics were similar to those found in the overall group of patients—in order to correlate the measures of normalized volumes of the brainstem, mesencephalus, pontine tegmentum, basis of pons, medulla oblongata, and cerebellum with BDI. More detailed procedures of the utilized technique were described elsewhere [9]. We found no significant correlations of MRI volumetries with BDI (data not shown).

Our data show a direct correlation of disease severity (measured by SARA and NESSCA) with depressive symptoms, and is in accordance with the results presented by Klinke et al. [1], although perhaps with slightly stronger evidence, since those authors reported only a trend toward correlation of BDI with SARA [1]. Our significance probably relied on a larger and more homogeneous sample of patients (only with SCA3), with worse SARA and BDI scores.

Considering SCA3 only, it is evident that our patients had longer disease duration and CAG repeat lengths than those described in that study [1]. One could argue that the higher depression scores could be related to the longer CAG expansions we saw, but we did not find any evidence of that. We found a correlation of BDI with disease duration;

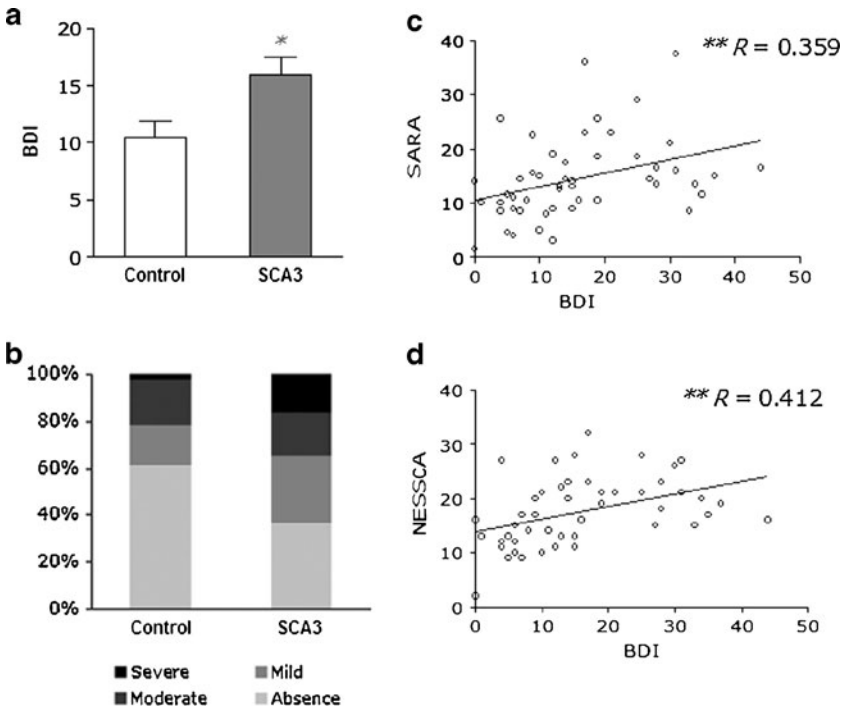

Fig. 1 Depression scores in SCA3. **a** BDI score in SCA3 patients and controls. **b** Representation (%) of the severity of BDI scores between groups. **c** Correlation of BDI with SARA and **d** correlation of BDI with NESSCA. Values are given as means and error bars represent standard error (SEM); *p<0.05; **p<0.01

however, this was likely to be a confounding factor relating larger disease durations with more severe ataxic scores. Lastly, sociocultural differences between Brazilians and Europeans should be borne in mind, although it is impossible to test for these.

Although these factors—mutation severity, disease duration, and cultural characteristics—are not mutually exclusive, the absence of any association between BDI and molecular findings or MRI normalized volumes, in our study, suggest that depression in SCA3 is not primarily related to brain involvement, but rather related to physical incapacity [1, 10].

Depressive symptoms are very common and significantly impair the quality of life of ataxic patients [3, 4]. At least in SCA3, patients may respond well to treatments aimed at improving the ways in which they deal with their disability, such as occupational therapy [11]. That our data support the view that depressive symptoms in SCA3 are not primarily related to the underlying pathological process could be a matter of debate. However—whether organic or reactive—depressive symptoms are an integral part of SCA3 deserving attention from the physicians who treat this disease.

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