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Short communication

A case series of hereditary cerebellar ataxias in a highly consanguineous population from Northeast Brazil

Deborah Moreira Rangel[a,b], Paulo Ribeiro Nóbrega[a,b], Maria Luiza Saraiva-Pereira[d,e], Laura Bannach Jardim[e,f], Pedro Braga-Neto[a,b,c,*]

[a] Division of Neurology, Department of Clinical Medicine, Universidade Federal do Ceará, Brazil
[b] Neurology Service, Hospital Geral de Fortaleza, Fortaleza, Ceará, Brazil
[c] Center of Health Sciences, Universidade Estadual do Ceará, Brazil
[d] Department of Biochemistry, Universidade Federal do Rio Grande do Sul, Brazil
[e] Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Rio Grande do Sul, Brazil
[f] Department of Internal Medicine, Universidade Federal do Rio Grande do Sul, Brazil

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ABSTRACT

Background: There are few studies reporting characteristics of patients with cerebellar ataxias in the Brazilian population. The aim of this study was to provide a detailed neurological description of patients with hereditary ataxia followed by a neurology outpatient service in Brazil.

Methods: Neurological and clinical evaluation of patients with hereditary ataxia was performed at a neurology service outpatient clinic of a hospital in Northeast Brazil between October 2013 and January 2015.

Results: A total of 47 patients had ataxia as the main symptom. A high prevalence of consanguinity was found in the population studied (40.4%). Mean age was 38.4 ± 15.3 years, mean age at disease onset was 25.6 ± 17.3 years, mean disease duration was 12.8 ± 9.7 years, and mean score on the Scale for the Assessment and Rating of Ataxia (SARA) was 18.4 ± 7.7. Patients with recessive pattern of inheritance were younger, had earlier age at disease onset and greater severity of ataxia, measured by the SARA. Diagnosis was confirmed by molecular analysis, laboratory exams or biopsy in 42.56% (n = 20) of these patients. The most prevalent diseases were: Friedreich's ataxia in 35% (n = 7), Niemann-Pick type C (NPC) in 15% (n = 3), and ataxia with oculomotor apraxia type 2 in 15% (n = 3).

Conclusions: In contrast with other studies, our prevalence of recessive ataxias was much higher than that of dominant ataxias. These findings might be explained by the high number of patients living in rural areas with a higher rate of consanguineous marriages, absence of a dominant ataxia founder effect or difficult access to healthcare system.

1. Introduction

Ataxias have genetic and non-genetic etiologies, and according to current etiology-based classifications, they can be subdivided into primary and secondary ataxias. Primary ataxias are hereditary ataxias and secondary ataxias include those due to exogenous or endogenous non-genetic causes [1].

There is scant knowledge on clinical phenotype and subtypes of hereditary ataxias in Brazil. Most descriptions of ataxia cohorts in Brazil are based on subjects from the Southeast and South metropolitan regions, where medical care is supported by a network of clinical genetic services [2,3].

In addition, diverse ethnic, geographic and cultural characteristics promote a huge variation, leading to our hypothesis that phenotype and genotype of hereditary ataxias may differ in the population from Northeast Brazil compared to other regions. The objective of the present study was to provide a detailed neurological description of patients with hereditary ataxia at a neurology outpatient service in Fortaleza, an important metropolis in this region of Brazil.

2. Methods

We evaluated patients followed at an outpatient movement disorders clinic between October 2013 and January 2015 located in

* Corresponding author. Universidade Federal do Ceará, Department of Clinical Medicine, Rua Prof. Costa Mendes, 1608, 4° andar - Rodolfo Teófilo, Fortaleza, Ceará, Brazil.
E-mail address: pbraganeto@ufc.br (P. Braga-Neto).

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Northeast Brazil. Ataxic patients were invited to participate in this study. Subjects with secondary ataxias (toxic, paraneoplastic, immune-mediated, nutritional, infectious, vascular, neoplastic or idiopathic ataxia) were excluded.

After signing of the consent form, patient demographic and clinical data were obtained by structured interview collecting information such as age, age at ataxia onset, disease duration since first symptom or start of gait ataxia, and family history. Consanguineous marriage was defined as a union between two individuals related as second-degree cousins or closer [4]. Cognitive outcomes were assessed by the Mini-Mental State Exam (MMSE). All patients were evaluated by a standard neurological examination and by the Scale for the Assessment and Rating of Ataxia (SARA). Electroneuromyography and neuroimaging features were also evaluated. Imaging techniques included computed tomography (CT) and/or magnetic resonance (MR) brain imaging. The cerebellum was carefully evaluated for the presence of atrophy.

According family history, ataxic patients were divided into two groups for diagnostic work-up. Patients (and families) with autosomal dominant (AD) inheritance were designated AD cases when a positive family history was reported across three or more consecutive generations for both genders. The AD group was studied for expansions in *ATXN1*, associated with spinocerebellar ataxia (SCA) type 1 (SCA1), *ATXN2* (associated with SCA2), *ATXN3* (associated with SCA3/MJD), *CACNA1A* (SCA6), *ATXN7* (SCA7), *ATXN10* (SCA10), *PPP2R2B* (SCA12), *TBP* (SCA17), and *ATN1* (DRPLA) genes.

Patients without autosomal dominant inheritance were denominated cases “without AD pedigree” (WADP). Alpha-fetoprotein testing was performed for all WADP cases. The suspicion index (SI) tool for Niemann-Pick type C (NPC) was applied and a detailed eye movement examination performed [5]. WADP individuals with a SI < 40 (low probability of having NPC) and without oculomotor apraxia were then first studied for the presence of GAA expansions in the *FXN* gene. Patients with repeat length within normal range were then included in the protocol for AD inheritance, as described earlier. Molecular diagnosis for spinocerebellar ataxias and Friedreich ataxia (FRDA) was performed at the same laboratory by the Neurogenetic Network (Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Brazil).

The Filipin test was performed in subjects with moderate-to high-SI scores (≥ 40). When positive, NPC1 and NPC2 genes were sequenced by Sanger analysis. Molecular analysis for NPC was also performed at the same laboratory (Medical Genetics Service, Hospital de Clínicas de Porto Alegre, Brazil). The full strategy is summarized in Fig. 1. Patients with AD inheritance ataxia and WADP with negative results were defined as unconfirmed diagnosis.

Molecular diagnosis for ataxia with oculomotor apraxia type 2 (AOA2), ataxia-telangiectasia, autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), and Cerebrotendinous xanthomatosis (CTX) were not performed. However, patients with elevated alpha-fetoprotein, ataxia, cerebellar atrophy and polyneuropathy were defined as having confirmed diagnosis of AOA2. Similarly, patients with elevated alpha-fetoprotein, ataxia, telangiectasias and low level of immunoglobulins were defined as having confirmed diagnosis of ataxia-telangiectasia. Finally, patients with clinical and neuroimaging features highly suggestive of ARSACS (superior vermis atrophy and linear hypointensities in the pons) and CTX (bilateral hyperintensity of the dentate nuclei and cerebral and cerebellar white matter) were also considered as having confirmed diagnosis for these diseases. For the latter cases, biopsy of xanthomas was also performed.

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 18. The presence of a normal distribution of data was determined by the Kolmogorov-Smirnov test. For normally distributed variables with homogeneity of variance, a two-tailed Student's *t*-test was performed. For variables that did not meet the homogeneity of variance requirement, the non-parametric Mann–Whitney *U* test was used. Categorical variables were analyzed by Fisher's exact test. Differences were considered statistically significant for $p < 0.05$. The local ethics committee approved this study under the registry number 693606.

3. Results

A total of 548 patients with movement disorders followed at our outpatient neurologic clinic were included in the neurological evaluation. Cerebellar ataxia was detected in 54 patients. Forty-seven patients (45 families) fulfilled inclusion criteria and were included in the sample, comprising seven (7 families) AD and 40 (38 families) WADP patients (Fig. 1). A high prevalence of consanguinity was found in the population studied (40.4%). The majority of patients (59.5%) were born in rural areas, and diagnosis was confirmed in 42.56% (Table 1).

Characteristics of AD cases and WADP groups are compared in Table 1. Patients in the WADP group were significantly younger, had significantly earlier onset of symptoms, and higher SARA scores. Although not statistically significant, consanguinity was more frequent in WADP cases, perhaps owing to the small sample of AD patients. There was also no statistical significance when comparing the confirmed recessive cases to confirmed AD patients ($p = 0.509$). All patients underwent neuroimaging, but brain MRI was performed in only 37 patients. Cerebellar atrophy was a frequent finding ($N = 24$; 51.1%). Eighteen patients underwent electroneuromyography and the most common pattern of polyneuropathy was axonal. Only one patient had sensorimotor demyelinating neuropathy.

Diagnosis was confirmed in two out of the seven AD patients: one as a SCA2 case and the other as a SCA3/MJD case. Unfortunately, we were unable to evaluate all family members of the patients with ataxia. Only 2 family members of patients WADP were diagnosed with FRDA and AOA2, respectively. Among WADP cases, autosomal recessive forms were the most frequent but not the only class of diagnosis: FRDA was the most frequent, followed by NPC and AOA. A high rate of patients with no definitive diagnosis was also found in WADP pedigrees with consanguineous marriages.

One WADP patient was diagnosed with SCA7. Her family history was negative. Neurological examination revealed gait ataxia, pyramidal findings and dysarthria. There was no complaint of visual loss and fundoscopy was normal.

Regarding clinical and neurological evaluations, over 80% of FRDA patients had Babinski's sign and cardiomyopathy. All NPC patients exhibited vertical gaze palsy, ataxia and cognitive decline. Cerebellar atrophy was present in all AOA2 patients and 2 out of the 3 cases had peripheral neuropathy.

4. Discussion

Eighteen of the 45 ataxic families were diagnosed as having a specific hereditary ataxia, 15 of which carried autosomal recessive disorders. The most common form was FRDA. Moreover, this study showed a high proportion of WADP in the overall group compared to AD forms. The high prevalence of consanguinity in the sample, mostly WADP subjects, is congruent with this unique characteristic of our series of patients. Since consanguinity rates are high in this population, we speculate that autosomal recessive forms of ataxia are indeed the most common in the population studied. Other reasons for our findings might be absence of a dominant ataxia founder effect in our population and difficult access to healthcare system where only the most severe recessive cases come to neurological attention.

In Northeast Brazil, particularly in rural and isolated areas, a high rate of consanguineous marriages is common. A study carried out in five cities of Rio Grande do Norte state reported 33% consanguineous marriages in one of the cities, Serrinha dos Pintos, a rural area of Northeast Brazil [6]. Our sample had a high percentage of patients from rural areas, explaining the high consanguinity rate found. In the Northeast region of Brazil, particularly in rural and isolated areas, a high rate of consanguineous marriages is common. Consanguineous

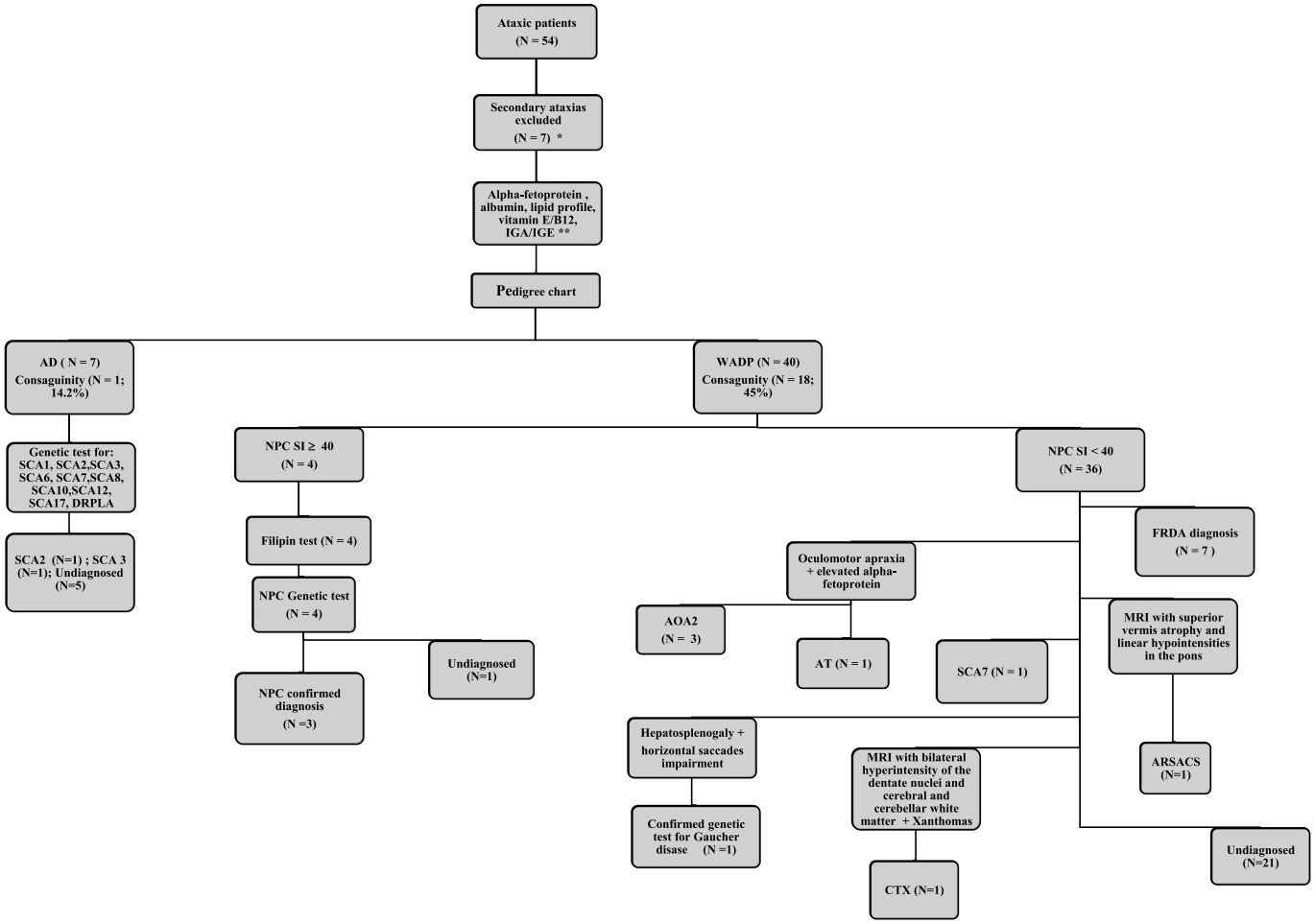

Fig. 1. Strategy for analysis of patients with hereditary ataxia.
AD: Autosomal dominant; **AOA2**: Ataxia with oculomotor apraxia type 2; **ARSACS**: Autosomal recessive spastic ataxia of Charlevoix-Saguenay**; AT**: Ataxia telangiectasia; **CTX**: Cerebrotendinous xanthomatosis; **DRPLA**: Dentatorubral-pallidoluysian atrophy; **FRDA**: Friedreich ataxia; **MRI**: Magnetic resonance imaging; **NPC**: Niemann-Pick type C; **SI**: suspicion index; **SCA1**: spinocerebellar ataxia type 1; **SCA2**: spinocerebellar ataxia type 2; **SCA3**: spinocerebellar ataxia type 3; **SCA6**: spinocerebellar ataxia type 6; **SCA7**: spinocerebellar ataxia type 7; **SCA8**: spinocerebellar ataxia type 8; **SCA10**: spinocerebellar ataxia type 10; **SCA12**: spinocerebellar ataxia type 12; **SCA17**: spinocerebellar ataxia type 17; **WADP**: without AD pedigree.
* Seven patients were excluded due to secondary or idiopathic causes of ataxia: 1 patient with Arnold-Chiari disease, 2 patients with Multiple System atrophy, 2 patients with acute post-infectious cerebellitis, 1 patient with anti-GAD related ataxia and 1 patient with ataxia related to phenytoin use.
** Other exams were performed when necessary.

marriages are associated with increased risk of autosomal recessive diseases [4]. Studies performed in other populations with high consanguinity rates also showed a high proportion of autosomal recessive ataxias, the most common of which was FRDA [7]. However, it is also important to consider that the high rate of autosomal recessive ataxia in our population may have been a result of the founder effect rather than consanguinity. The state of Ceará was colonized mainly by Portuguese families, and might have involved different families to those in the Southern region of Brazil, which was first settled by Azoreans and where SCA3 clearly represents a founder effect.

Previous global studies have described dominant ataxias as being more prevalent than, or at least as frequent as, recessive ataxias [8]. In Brazil, the prevalence of recessive ataxias has never been determined, whereas the prevalence of dominant ataxias has been estimated at 2.0–6.5 per 100,000 population [9].

In our cohort, FRDA was the most frequent recessive ataxia, accounting for five out of the 15 familial diagnoses. However, two of these five FRDA index-cases had a presumptive diagnosis, based on the identification of only one allele carrying a GAA expansion. We presumed that the other allele carried an unidentified mutation and subjects would therefore be compound heterozygotes, as described previously [10]. The clinical picture of these cases was highly characteristic of the common phenotype. Both patients had ataxia, polyneuropathy, bilateral Babinski sign and absence of cerebellar atrophy. Moreover, one patient had a positive family history of FRDA.

Surprisingly, only three patients with dominant ataxias were identified in our sample: SCA2, SCA3 and SCA7. The other five ataxic subjects with AD history (71%) remained undiagnosed. A study of 359 families with AD ataxia from 11 cities in Brazil described SCA3/MJD as the leading cause (59.6%), followed by SCA2 (7.8%); only 65 SCA families (or 18.1%) were undiagnosed. In a separate analysis of the Northeastern population, the number of undiagnosed patients was higher at 64% [11]. Although the proportion of undiagnosed SCAs is large (71%) and might have been due to the small number of cases in the present cohort, this finding replicates previous results and might suggest that a form of SCA, rare in other populations, exists in Northeast Brazil.

The diagnostic work-up for inherited ataxias can be complex. Since carriers of dominant forms sometimes have a negative family history, isolated (or sporadic) cases should be investigated for both recessive and dominant traits, such as SCAs. In the present study, such patients were included in the WADP group, and a carrier of an expansion in the

Table 1
Clinical and demographic characteristics of hereditary ataxia patients and comparison between AD and WADP groups.

	Total Hereditary ataxia cohort N = 47	WADP N = 40	AD N = 7	p
Age (years); mean ± SD	38.4 ± 15.3	36.3 ± 15.1	50.8 ± 10.8	0.022[a]
Sex (M/F); % F	21/26; 55.31%	17/23; 57.5%	4/3; 57.1%	0.684[b]
Age at disease onset; mean ± SD	25.6 ± 17.5	22.5 ± 16.5	43.8 ± 11.4	**0.002***[a]
Disease duration; mean ± SD	12.8 ± 9.7	13.8 ± 10.1	7 ± 3.4	0.080[a]
SARA; mean ± SD	18.4 ± 7.7	19.5 ± 7.5	11.9 ± 6.6	**0.018***[a]
Family history; n (%)	23 (48.9%)	16 (40%)	7 (100%)	**0.04***
Born in rural areas; n (%)	28 (59.5%)	23 (57.5%)	5 (71.42%)	0.488
Consanguinity; n (%)	19 (40.4%)	18 (45%)	1 (14.2%)	0.133[b]
Peripheral neuropathy; n (%)	20 (42.5%)	17 (42.5%)	3 (42.8%)	0.648[b]
Brisk reflexes; n (%)	21 (44.6%)	19 (47.5%)	2(28.5%)	0.307[b]
Babinski sign; n (%)	22 (46.8%)	19 (47.5%)	3 (42.8%)	0.574[b]
Vertical gaze palsy; n (%)	9 (19.14%)	9 (22.5%)	0 (0%)	0.318[b]
Ocular apraxia; n (%)	7 (14.89%)	6 (15%)	1 (14.2%)	0.724[b]
Cardiopathy; n (%)	6 (12.76%)	6 (15%)	0 (0%)	0.357[b]
Epilepsy; n (%)	12 (25.53%)	9 (22.5%)	3 (42.8%)	0.243[b]
Cognitive decline; n (%)	15 (31.9%)	14 (35%)	1(16.6%)	0.404[b]
Cerebellar atrophy on MRI; n (%)	24 (51.1%)	20 (50%)	4 (57.1%)	0.652[b]
Confirmed diagnosis; n (%)	20 (42.55%)	18 (45%)	2 (14.2%)	0.229[b]

M: Male; F: Female; SARA: Scale for the Assessment and Rating of Ataxia; SD: standard deviation; WADP: without autosomal dominant pedigree; AD: autosomal dominant.
* Statistically significant (comparison between AD and WADP patients).
[a] Mann-Whitney test.
[b] Fisher test.

ATXN7 gene was found among the 38 WADP families.

The present study has some limitations such as the small sample size, hampering the detection of differences between subgroups. Data reported here reveal few patients with a confirmed diagnosis, where rates proved lower than some studies yet higher than others. This may be due to the low number of genetic tests to investigate recessive forms of ataxia included in the study. The genetic assessment of other recessive ataxias (*SYNE1*, SPG7, AOA2, AT and CTX) could have significantly increased the number of patients with confirmed diagnosis.

Moreover, genetic evaluation of patients' families was not performed. The genetic profile of the families could have yielded further information on the undiagnosed patients. A more comprehensive genetic assessment, including whole exome sequencing (WES), could provide a broader range of genes, consequently increasing the number of patients with specific diagnosis. An alternative approach might be comprehensive gene panels, which could reduce costs both in terms of reagents and interpretation [12].

Over the course of years, molecular characterization of neurogenetic disorders has moved from being a primary research interest to one of clinical diagnosis and potentially of developing specific therapies. Diagnosing hereditary ataxia in areas where molecular diagnosis is not yet widely available remains a clinical challenge. Despite the drawbacks outlined above, patients lacking a proper diagnosis exist worldwide, including in resource-deprived areas. Therefore, sharing experiences and strategies can be enlightening for centers located in these areas. The establishment of international genetic cooperative work groups and local cost-effective genetic testing can increase the diagnosis of hereditary ataxias in developing countries.

Declarations

Ethics approval and consent to participate

Informed consent to present and publish medical data was obtained from all patients. The local ethics committees approved this study under registry number 693606.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article. The datasets analyzed are available from the corresponding author.

Authors' roles

DMR participated in study conception and design, acquisition of the raw data, analysis and interpretation of the data, and drafting of the study.

PRN participated in acquisition of the raw data, analysis and interpretation of the data and critical review of the manuscript.

MLSP and LBJ participated in acquisition of the raw data, drafting of the study and critical review of the manuscript.

PBN participated in study conception and design, acquisition of the raw data, analysis and interpretation of the data, drafting of the study and critical review of the manuscript.

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Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Financial disclosure

We have nothing to disclose.

Ethical statement

Patients signed an informed consent form and allowed publication of this data.

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