Article published online: 2024-07-04

Ataxias in Brazil: 17 years of experience in an ataxia center

Ataxias no Brasil: 17 anos de experiência em um centro de ataxias

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Arq. Neuro-Psiquiatr. 2024;82(8):s00441787800.

Abstract

Background Cerebellar ataxias comprise sporadic and genetic etiologies. Ataxia may also be a presenting feature in hereditary spastic paraplegias (HSPs).

Objective To report a descriptive analysis of the frequency of different forms of cerebellar ataxia evaluated over 17 years in the Ataxia Unit of Universidade Federal de São Paulo, Brazil.

Methods Charts of patients who were being followed from January 2007 to December 2023 were reviewed. We used descriptive statistics to present our results as frequencies and percentages of the overall analysis. Diagnosed patients were classified according to the following 9 groups: sporadic ataxia, spinocerebellar ataxias (SCAs), other autosomal dominant cerebellar ataxias, autosomal recessive cerebellar ataxias (ARCAs), mitochondrial ataxias, congenital ataxias, X-linked ataxias, HSPs, and others.

Results There were 1,332 patients with ataxias or spastic paraplegias. Overall, 744 (55.85%) of all cases were successfully diagnosed: 101 sporadic ataxia, 326 SCAs, 20 of other autosomal dominant cerebellar ataxias, 186 ARCAs, 6 X-linked ataxias, 2 mitochondrial ataxias, 4 congenital ataxias, and 51 HSPs.

Conclusion This study describes the frequency of cerebellar ataxias in a large group of patients followed for the past 17 years, of whom 55% obtained a definitive clinical or molecular diagnosis. Future demographic surveys in Brazil or Latin American remain necessary.

Keywords
- Ataxia
- Spastic Paraplegia, Hereditary
- Demography
- Movement Disorders

received
February 26, 2024
received in its final form
April 10, 2024
accepted
April 25, 2024

DOI https://doi.org/10.1055/s-0044-1787800.
ISSN 0004-282X.

Editor-in-Chief: Hélio A. G. Teive.
Associate Editor: Renato Puppi Munhoz.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Resumo

Antecedentes Ataxias cerebelares compreendem as etiologias esporádicas e genéticas. Ataxia também pode ser uma característica das paraplegias espásticas hereditárias (HSPs).

Objetivo Relatar uma análise descritiva da frequência das diferentes formas de ataxias cerebelares avaliadas ao longo de 17 anos no Setor da Ataxias da Universidade Federal de São Paulo, Brasil.

Métodos Prontuários de pacientes acompanhados de janeiro de 2007 a dezembro de 2023 foram revisados. Usamos análise descritiva para apresentar nossos resultados como frequências e percentuais. Os pacientes foram classificados de acordo com os 9 grupos seguintes: ataxias esporádicas, ataxias espinocerebelares (SCA), outras ataxias cerebelares autossômicas dominantes, ataxias cerebelares autossômicas recessivas (ARCA), ataxias mitocondriais, ataxias congênitas, ataxias ligadas ao X, PEH e outros.

Resultados Foram avaliados 1.332 pacientes. Desse total, 744 (55,85%) tiveram um diagnóstico definitivo: 101 ataxias esporádicas, 326 SCA, 20 outras ataxias cerebelares autossômicas dominantes, 186 (ARCA), 6 ataxias ligadas ao X, 2 ataxias mitocondriais, 4 ataxias congênitas e 51 HSP.

Conclusão Esse estudo descreve a frequência e a etiologia das ataxias em um grande grupo de pacientes acompanhados nos últimos 17 anos, dos quais 55% obtiveram diagnóstico clínico ou molecular definitivos. Estudos demográficos futuros do Brasil ou da América Latina continuam sendo necessários.

Palavras-chave

- Ataxia
- Paraplegia Espástica Hereditária
- Demografia
- Transtornos dos Movimentos

INTRODUCTION

Clinically, the term *ataxia* denotes incoordination and loss of balance,[1] which is a hallmark of degenerative disorders that mainly target the cerebellum.[1] Cerebellar ataxias are a heterogeneous group of diseases comprising sporadic ataxias and genetic etiologies.[2] The sporadic ataxias group is characterized by adult-onset ataxias, usually over 40-years-old, with no family history for ataxia or its related symptoms and signs.[2]

Ataxia may also be a presenting feature in hereditary spastic paraplegias (HSPs) and other neurological disorders.[3] Genetic cerebellar ataxias and HSPs are rare neurodegenerative disorders, generally related to degeneration of the cerebellum and its connections.[4] Additionally, they share considerable clinical overlap, presenting progressive gait impairment, permanent disability, and premature death.[5]

The frequency of these diseases in different populations and their natural history are relevant knowledge for health authorities to develop care strategies.[6,7] Nevertheless, it is worth mentioning that epidemiological data on these disorders are scarce, particularly in underdeveloped countries. Hence, their true global distribution and prevalence remains uncertain.[8] Moreover, regardless the recent advances of diagnostic genetic techniques, the genetic diagnosis of most patients is still undefined.[6]

In this original article, we perform a descriptive analysis of the frequency and etiology of sporadic ataxias, genetic cerebellar ataxias, and HSPs, evaluated over 17 years in a reference center of ataxia in São Paulo, Brazil.

METHODS

We present a cross-sectional and monocentric study of 1,332 heterogenous patients with ataxia or spastic paraplegias that were referred to our service, the Ataxia Unit at Hospital São Paulo, from Universidade Federal de São Paulo, Brazil. To describe epidemiological and genetic features, two independent investigators (BKM and MTDG) reviewed medical records of patients who were being followed from January 2007 to December 2023. Data were independently reviewed by the authors and disagreements were resolved through discussion until a consensus was reached. The approval of an institutional review board was not required for this research.

Diagnosed patients were classified accordingly to the following nine groups: sporadic ataxias, spinocerebellar ataxias (SCAs), other autosomal dominant cerebellar ataxias, autosomal recessive cerebellar ataxias (ARCAs), mitochondrial ataxias, congenital ataxias, X-linked ataxias, HSPs, and others. Patients were included based on the following criteria: diagnosis of sporadic ataxias according to the appropriate diagnostic criteria at the time of medical evaluation;[1] definitive diagnosis of hereditary genetic diseases were considered only with genetic confirmation for each case. Furthermore, patients with incomplete data preventing confirmation of any specific disease were excluded. We used descriptive statistics to present our results as frequencies and percentages of the overall analysis.

RESULTS

►**Table 1** summarizes the main data concerning demographics of this study. Overall, there were 1,332 patients, of whom 689 were women (51.72%), and 744 (55.85%) had their diagnostic confirmed by genetic testing or appropriate criteria. Among the diagnosed group, there were sporadic ataxias ($n = 101$; 7.58%), SCAs ($n = 326$; 24.47%), other autosomal dominant cerebellar ataxias ($n = 20$; 1.50%), ARCAs ($n = 186$; 13.96%), X-linked ataxias ($n = 6$; 0.45%), mitochondrial ataxias ($n = 2$; 0.15%), congenital ataxias ($n = 4$; 0.30%), HSPs ($n = 51$; 3.82%), and other ($n = 48$; 3.60%). It is important to note that the analysis of 23 patients showed variants of uncertain significance (VUSs). The frequency of patients included in each of the different categories of neurological diseases is detailed in ►**Table 2**.

With regard to the sporadic ataxia group, the most common diagnosis was multiple system atrophy (MSA) ($n = 51$), followed by cerebellar alcohol degeneration ($n = 12$), anti-glutamic acid decarboxylase (GAD; $n = 4$), Chiari malformation type 1 ($n = 4$), HIV ($n = 3$), infections ($n = 3$), stroke ($n = 3$), and vitamin B12 deficiency ($n = 3$). It is worth mentioning that there were 8 immune-mediated cerebellar ataxias, including the Sjogren syndrome ($n = 2$), as well as the neuronal antigens anti-GAD ($n = 4$), anti-Hu ($n = 1$), and anti-Yo ($n = 1$).

In the SCAs group, the most frequent was SCA-3 ($n = 170$), followed by 2 ($n = 60$), 7 ($n = 39$), 1 ($n = 29$), 6 ($n = 17$), 10 ($n = 3$), and 31 ($n = 3$). There were also single cases of SCA5, 21, 27, 28, and 42. Among the other autosomal dominant cerebellar ataxias group, there were cases of Gerstmann-Sträussler-Scheinker ($n = 7$); dentatorubral-pallidoluysian atrophy (DRPLA, $n = 2$); episodic ataxia type 2 ($n = 2$); autosomal dominant cerebellar ataxia, deafness, and narcolepsy (ADCADN, $n = 1$); autosomal dominant adult-onset demyelinating leukodystrophy (ADLD, $n = 1$); Alexander disease ($n = 1$); ataxia-pancitopenia ($n = 1$); developmental and epileptic encephalopathy 42 (DEE42, $n = 1$); fatal familial insomnia ($n = 1$); hereditary diffuse leukoencephalopathy with spheroids 1 (HDLS1, $n = 1$); Kleefstra syndrome-2 (KLEFS2; $n = 1$); and neurodegeneration and spasticity with or without cerebellar atrophy or cortical visual impairment (NESCAV syndrome, $n = 1$).

Concerning the ARCAs group, Friedreich ataxia (FRDA) was the most frequent diagnosis ($n = 82$), followed by ataxia-telangiectasia ($n = 28$), cerebellar ataxia, neuropathy, and vestibular areflexia syndrome (CANVAS; $n = 12$), autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS; $n = 9$), spectrin repeat-containing nuclear envelope protein 1 (SYNE1; $n = 9$), ataxia-oculomotor apraxia 2 (AOA2; $n = 6$), Niemann-Pick disease type C1 ($n = 4$), ataxia-oculomotor apraxia 4 (AOA4; $n = 3$), ataxia-oculomotor apraxia 1 ($n = 2$), autosomal recessive spinocerebellar ataxia-10 (SCAR10; $n = 2$), ceroid lipofuscinosis 2 ($n = 2$), neurodegeneration with brain iron accumulation 1 (NBIA-1; $n = 2$); NBIA-2A ($n = 2$); RNA polymerase III subunit A-related (POLR3A-related) ($n = 2$), primary coenzyme Q10 deficiency ($n = 2$), and ataxia-telangiectasia-like disorder-1 ($n = 2$).

The congenital ataxias group was represented by Gomez-Lopez-Hernandez ($n = 1$), leukodystrophy hypomyelinating 6 ($n = 1$), premature birth ($n = 1$), and succinic semialdehyde dehydronenase deficiency ($n = 1$). About the X-linked ataxias group, we found adrenoleukodystrophy ($n = 4$), adrenomyeloneuropathy ($n = 1$), and Mohr-Tranebjaerg ($n = 1$). The mitochondrial ataxias group was composed by the Kearns-Sayre ($n = 1$) and Leigh syndromes ($n = 1$).

Among the patients diagnosed with HSPs ($n = 51$), we identified 17 autosomal dominant HSPs, including cases of spastic paraplegia 4 (SPG-4; $n = 11$), 3A ($n = 3$), 31 ($n = 2$), and 10 ($n = 1$). Among the 34 autosomal recessive HSPs, the most frequent was SPG-11 ($n = 16$), followed by 7 ($n = 9$), 15 ($n = 4$), 76 ($n = 2$), 78 ($n = 2$), and 35 ($n = 1$).

There were 48 other cases not related to sporadic ataxias, hereditary cerebellar ataxias, or HSPs. It was composed by functional neurological disorders ($n = 14$), Huntington disease ($n = 13$), essential tremor ($n = 3$), progressive supranuclar palsy ($n = 3$), chronic nonprogressive encephalopathy ($n = 2$), and vestibular dizziness ($n = 2$). Moreover, diseases related to the actin beta (*ACTB*) and presenilin 1 (*PSEN1*) genes, amyotrophic lateral sclerosis, congenital myasthenic syndrome 12, myoclonic dystonia-11 (DYT11), rapid-onset dystonia-parkinsonism (DYT12), epilepsy, Parkinson's disease, hypomelanosis of Ito, tropical spastic paraparesis, and vascular parkinsonism represented one case each.

Table 1 Demographics of the study sample

Demographics	N (%)
Total cases	1,332 (100.00)
Female subjects	689 (51.72)
Diagnosed cases	744 (55.85)
Sporadic ataxias	101 (7.58)
Spinocerebellar ataxias	326 (24.47)
Other autosomal dominant cerebellar ataxias	20 (1.50)
Autosomal recessive cerebellar ataxias	186 (13.96)
X-linked ataxias	6 (0.45)
Congenital ataxias	4 (0.30)
Mitochondrial ataxias	2 (0.15)
Hereditary spastic paraplegias	51 (3.82)
Others	48 (3.60)
Variant of uncertain significance	23 (1.72)

DISCUSSION

In this study we report the main epidemiological features of 1,332 patients with ataxias or spastic paraplegias. Overall, 744 (55.85%) of all cases were successfully diagnosed. In brief, the diagnosis rates of each group were: sporadic ataxias ($n = 101$; 7.58%), SCAs ($n = 326$; 24.47%), other autosomal dominant cerebellar ataxias ($n = 20$; 1.50%), ARCAs ($n = 186$; 13.96%), X-linked ataxias ($n = 6$; 0.45%), mitochondrial

Table 2 Demographics of the diagnosed cases ($N = 744$)

Disease	N (%)	Disease	N (%)
Sporadic ataxias	**101 (100.00)**	**Autosomal recessive cerebellar ataxias**	**186 (100.00)**
Multiple system atrophy	51 (50.49)	Friedreich ataxia	82 (44.08)
Cerebellar alcohol degeneration	12 (11.88)	Ataxia-telangiectasia	28 (15.05)
Anti-GAD	4 (3.96)	CANVAS	12 (6.45)
Chiari malformation type 1	4 (3.96)	ARSACS	9 (4.83)
HIV	3 (2.97)	SYNE1	9 (4.83)
Infections	3 (2.97)	Ataxia-oculomotor apraxia-2	6 (3.22)
Stroke	3 (2.97)	Niemann-Pick disease type C1	4 (2.15)
Vitamin B12 deficiency	3 (2.97)	Ataxia-oculomotor apraxia-4	3 (1.61)
Multiple sclerosis	2 (1.98)	Ataxia-oculomotor apraxia-1	2 (1.07)
Sjögren syndrome	2 (1.98)	SCAR10	2 (1.07)
Superficial siderosis	2 (1.98)	Ataxia-telangiectasia-like disorder-1	2 (1.07)
Anti-Hu	1 (0.99)	Ceroid lipofuscinosis-2	2 (1.07)
Anti-Yo	1 (0.99)	NBIA1	2 (1.07)
Cavernoma	1 (0.99)	NBIA2A	2 (1.07)
Cerebral amyloid angiopathy	1 (0.99)	POLR3A-related	2 (1.07)
Hypermanganesemia	1 (0.99)	Primary coenzyme Q10 deficiency	2 (1.07)
Idiopathic late onset cerebellar ataxia	1 (0.99)	Ataxia-telangiectasia-like disorder-1 4H syndrome	2 (1.07)
Mercury intoxication	1 (0.99)	4H syndrome	1 (0.53)
Müller-Fischer	1 (0.99)	Ataxia with vitamin E deficiency	1 (0.53)
Phenytoin progressive ataxia and palatal tremor	1 (0.99)	Ceroid lipofuscinosis-11	1 (0.53)
Progressive ataxia and palatal tremor	1 (0.99)	Ceroid lipofuscinosis-8	1 (0.53)
Syphilis	1 (0.99)	Cerebrotendinous xanthomatosis	1 (0.53)
Wernicke encephalopathy	1 (0.99)	COQ10D1	1 (0.53)
Spinocerebellar ataxias	**326 (100.00)**	COQ10D4	1 (0.53)
SCA3	170 (52.14)	Gillespie syndrome	1 (0.53)
SCA2	60 (18.40)	GM2-gangliosidosis	1 (0.53)
SCA7	39 (11.96)	NBIA4	1 (0.53)
SCA1	29 (8.89)	Oliver-McFarlane syndrome	1 (0.53)
SCA6	17 (5.21)	Sandhoff disease	1 (0.53)
SCA10	3 (0.92)	SANDO	1 (0.53)
SCA31	3 (0.92)	SeSAME	1 (0.53)
SCA5	1 (0.30)	Sialidosis type I	1 (0.53)
SCA21	1 (0.30)	VWM5	1 (0.53)
SCA27	1 (0.30)	**Others**	**48 (100.00)**
SCA28	1 (0.30)	Functional neurological disorder	14 (29.16)
SCA42	1 (0.30)	Huntington disease	13 (27.08)
Other autosomal dominant cerebellar ataxias	**20 (100.00)**	Essential tremor	3 (6.25)
Gerstmann-Sträussler-Scheinker	7 (35.00)	Progressive supranuclear palsy	3 (6.25)
Dentatorubro-pallidoluysian atrophy	2 (10.00)	Chronic non-progressive encephalopathy	2 (4.16)
Episodic ataxia type 2	2 (10.00)	Vestibular dizziness	2 (4.16)
ADCADN	1 (5.00)	*ACTB*-related	1 (2.08)

Table 2 (*Continued*)

Disease	N (%)	Disease	N (%)
ADLD	1 (5.00)	Congenital myasthenic syndrome-12	1 (2.08)
Alexander disease	1 (5.00)	Myoclonic dystonia-11 (DYT11)	1 (2.08)
Ataxia-pancitopenia	1 (5.00)	Rapid-onset dystonia-parkinsonism (DYT12)	1 (2.08)
Developmental and epileptic encephalopathy 42	1 (5.00)	Amyotrophic lateral sclerosis	1 (2.08)
Fatal familial insomnia	1 (5.00)	Epilepsy	1 (2.08)
HDLS1	1 (5.00)	Hypomelanosis of Ito	1 (2.08)
Kleefstra syndrome 2	1 (5.00)	Parkinson's disease	1 (2.08)
NESCAV syndrome	1 (5.00)	*PSEN1*-related	1 (2.08)
Congenital ataxias	**4 (100.00)**	Tropical spastic paraparesis	1 (2.08)
Gomez-Lopez-Hernandez	1 (25.00)	Vascular parkinsonism	1 (2.08)
HLD6	1 (25.00)	**Hereditary spastic paraplegias**	**51 (100.00)**
Premature birth	1 (25.00)	SPG11	16 (31.37)
SSADHD	1 (25.00)	SPG4	11 (21.56)
X-linked ataxias	**6 (100.00)**	SPG7	9 (17.64)
Adrenoleukodystrophy	4 (66.66)	SPG15	4 (7.84)
Adrenomyeloneuropathy	1 (16.66)	SPG3A	3 (5.88)
Mohr-Tranebjaerg	1 (16.66)	SPG31	2 (3.92)
Mitochondrial ataxias	**2 (100.00)**	SPG76	2 (3.92)
Kearns-Sayre	1 (50.00)	SPG78	2 (3.92)
Leigh syndrome	1 (50.00)	SPG10	1 (1.96)
		SPG35	1 (1.96)

Abbreviations: *ACTB*, actin beta; ADCADN, autosomal dominant cerebellar ataxia, deafness, and narcolepsy; ADLD, autosomal dominant adult-onset demyelinating leukodystrophy; ARSACS, autosomal recessive spastic ataxia of Charlevoix-Saguenay; CANVAS, cerebellar ataxia, neuropathy, and vestibular areflexia syndrome; COQ10D1, coenzyme Q10 deficiency-1; COQ10D4, coenzyme Q10 deficiency-4; GAD, glutamic acid decarboxylase; HDLS1, hereditary diffuse leukoencephalopathy with spheroids-1; HIV, human immunodeficiency virus; HLD6, hypomyelinating leykodystrophy-6; NESCAV, neurodegeneration and spasticity with or without cerebellar atrophy or cortical visual impairment; NBIA1, neurodegeneration with brain iron accumulation 1; NBIA2A, neurodegeneration with brain iron accumulation 2A; NBIA4, neurodegeneration with brain iron accumulation 4; POLR3A, RNA polymerase III subunit A; *PSEN1*, presenilin 1; SANDO, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis; SCAR10, autosomal recessive spinocerebellar ataxia of type 10; SeSAME, seizures, sensorineural deafness, ataxia, mental retardation, and electrolyte imbalance; SPG, spastic paraplegias; SSADHD, succinic semialdehyde dehydrogenase deficiency; SYNE1, synaptic nuclear envelope protein 1; VWM5, leukoencephalopathy with vanishing white matter-5.

ataxias ($n = 2$; 0.15%), congenital ataxias ($n = 4$; 0.30%), and HSPs ($n = 51$; 3.82%). Collectively, the most frequent causes were SCA3 ($n = 179$), FDRA ($n = 82$), SCA2 ($n = 60$), MSA ($n = 51$), and SCA7 ($n = 39$).

Autosomal dominant cerebellar ataxias comprehend a group of progressive adult-onset gait ataxia, dysmetria, and dysarthria associated with cerebellar atrophy on brain imaging.[9] The most frequent group is SCA, with over fifty distinct types clinically described (SCA1–50).[10,11] Other autosomal dominant cerebellar ataxias comprise episodic ataxias, spastic ataxias, and a complex form (dentatorubral-pallidoluysian atrophy, DRPLA). The frequency of individual subtypes of autosomal dominant cerebellar ataxias varies according to geographic region. The global prevalence of SCAs varies from 2 to 43 in 100 thousand people.[8,12,13] One cannot generalize these frequencies of each autosomal dominant cerebellar ataxias, due to significant background ethnicity among the Brazilian regions.[14] This study showed 326 cases of diagnosed SCAs, and the most frequent was type 3 ($n = 70$; 52.14%), what is in line to previous epidemiological studies about SCAs in the Brazilian population.[15–19]

Among SCAs, type 6 represents 31% of cases in Japan and 15% in the United States.[20–24] Teive et al.'s study reported 355 patients diagnosed with SCAs in southern of Brazil, of which 6 was the sixth most frequent type, representing 0.65% of the cases.[25] Type 6 is relatively uncommon in the Brazilian population, with a prevalence of 1.5 to 1.8%.[26,27] However, we found a 5.21% prevalence of SCA6 in our group. Among the 17 patients with type 6, 15 were Japanese descendants, but only 2 of them have Italian ancestry. This interesting higher prevalence of SCA6 of our population is probably because the city of São Paulo has been the main migration destination of Japanese people outside Japan. Additionally, there were three Brazilian siblings from Japanese lineage

with SCA31. Our findings suggest that familial, late-onset, pure cerebellar symptoms, variably associated with hearing impairment, should be tested for SCA31 particularly if there is Japanese ancestry and negative test results for type 6.[28]

Recently, ARCAs are classified into primary ARCAs and the group of other metabolic or complex autosomal recessive disorders that have ataxia as an associated feature.[3] Consistently, FRDA has been recognized as the most common cause of ARCAs worldwide, with an estimated prevalence of 1 to 2 cases every 100,000 people.[5,8,29] The second most common cause of ataxia varies between AOA and AT, depending on the study that is considered.[5,6,29] In our study, FDRA was the most prevalent ARCAs (44.08%), followed by AT (15.05%), which is consistent with the literature.

Sporadic ataxias are adult-onset nonfamilial progressive ataxias.[1] In the present study, the most common sporadic ataxia was MSA ($n = 51$; 50.49%). The estimated annual prevalence of this disease is 3 cases every 100 thousand people in populations over 50 years.[1] MSA is the diagnosis of up to 24% of sporadic adult onset ataxia patients within 4 to 5 years.[30,31] Furthermore, there were 8 immune-mediated cerebellar ataxias, including 6 related to neuronal antigens anti-GAD ($n = 4$), anti-Hu ($n = 1$), and anti-Yo ($n = 1$). Cerebellar ataxia may be the initial manifestation of autoimmune encephalitis, as the cerebellum is an important immunological target.[1] Thus, there was suspicion of an immune-mediated cerebellar ataxia, precluding screening for antineuronal antibodies, including autoimmune and paraneoplastic panels.[32]

The current study shows a local epidemiological analysis of ataxias in the Brazilian population, with patients evaluated in the state of São Paulo. Among the 1,156 patients with known place of residence that were referred to the center in search for the diagnosis and the adequate genetic test, the geographic distribution of patients by each region of Brazil are as follows: North ($n = 29$), Northeast ($n = 28$), Central-West ($n = 15$), Southeast ($n = 1{,}068$), and South ($n = 16$). Moreover, among the 808 patients with known state of birth and place of residence, 211 of them had moved to São Paulo at the time of their first evaluation. This difference between the state of birth and residence may help to illustrate the intense migration over different regions of Brazil, which certainly contributes to the difficult task of having a unique Brazilian demographic panorama of hereditary diseases. Although this could represent a limitation, it illustrates the regional heterogenous genetic background, differing from the United States/Europe.[33]

Our findings also have practical relevance. From a diagnostic perspective, these diseases remain a challenge for neurologists. Although the overall frequence of many diseases discussed above in the general population might be relatively low, they still should not be dismissed. A high level of suspicion for these disorders is vital to reach diagnosis. Besides the obstacle of the clinical suspicion, molecular tests are important bottlenecks to the etiological diagnosis of complex genetic disorders, such as ataxias and HSPs. The first problem is the limited access to genetic tests due to their high cost, especially in a developing country like Brazil. Second, there is the decision of which test is more suitable in the clinical setting to avoid unnecessary expendings and misinterpretations (such as triplet repeat primed polymerase chain reaction [TP-PCR] for repeat-expansion disorders, such as FRDA, and the most common forms of SCA). The third challenge to note is the necessity of periodic reanalysis of inconclusive tests and VUSs, due to the constant renewal of scientific knowledge with the discovery of new causative genes, molecular pathways, and other pathogenic mechanisms.

Overall, despite the difficulties, the etiological diagnosis should be thoroughly pursued, as patients can benefit both individually and collectively. On the individual level, the etiology allows a more accurate and personalized genetic counselling, by elucidating the pattern of inheritance, predicting risk of future offspring of developing the disorder, designing strategies to minimize this risk, and, for some conditions, specific therapeutic options shall be discussed. Collectively, there must be several benefits from research projects and drug trials that may only be possible if a considerable number of patients are diagnosed.

Our study has some limitations. We analyzed diagnostic frequencies for reference purposes only. Additionally, it should be noted that we did not characterize the phenotype of each case. All descriptive data was not exclusive of isolated patients. Consequently, the occurrence of possible family clusters of hereditary disease may have to be considered to forward prevalence conclusions. Comparison of our findings with other series of neurological outpatients is difficult since historically our service focuses on ataxia patients, and just recently has added a predilection to spastic paraplegias.

In summary, 55% of the patients included in this survey reached a definitive diagnosis. The goal of the study was to provide a descriptive analysis of the prevalence ataxias and HSPs that have being evaluated over 17 years in our Ataxia Unit in the state of São Paulo, Brazil. There is still much to discover about the molecular basis of these diseases with high genetic heterogeneity.[5,25] Future population-based systematic surveys in Brazil or Latin American remain necessary.

Authors' Contributions

BKM, MTDG: conceptualization, data curation, formal analysis, investigation, methodology, and writing of the original draft; TYT: data curation, formal analysis, and investigation; PBN, JLP, OGPB: project administration, supervision, and writing – review and editing.

Support

The author PBN received funding from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) as research grant funding (productivity scholarship). The authors declare that there are no additional disclosures to report.

Conflict of Interest

The authors have no conflict of interest to declare.

Acknowledgments

The authors deeply appreciate all the colleagues who cooperatively evaluated the patients over these 17 years,

particularly Adriana Dourado Rueda, Agessandro Abrahão Junior, Augusto Bragança Reis Rosa, Cristina Saade Jaques, Fabiano Ferreira de Abrantes, Fernanda Aparecida Maggi, Flávio Moura Rezende Filho, Giovana Lúcia Azevedo Diaféria, Ivana Rocha Raslan, Julian Leticia de Freitas, Juliana Harumi Arita, Karyme Hussein Daghastanli, Luane Abdalla Gouvea, Marcus Vinicius Cristino Albuquerque, Paola Lemos, Paula Camila Alves de Assis Pereira Matos, Rubens Paulo Araujo Salomão, Sophia Caldas Gonzaga da Costa, and Vinicius Boaratti Ciarlariello. The author Pedro Braga Neto received funding from the Brazilian National Council for Scientific and Technological Development (CNPq) as a research grant (productivity scholarship).

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