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Ataxias in Brazil

Ataxias no Brazil

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Ataxia is a neurological manifestation characterized by the loss of truncal balance and incoordination of limbs. Among various neurological diseases presenting with ataxia as the main symptom, neurodegenerative diseases comprise the majority, which are usually classified as sporadic and hereditary ataxias from the viewpoint of genetics. Hereditary ataxias are further classified on the basis of the mode of inheritance into diseases with autosomal dominant, autosomal recessive, and X-linked inheritances. Hereditary spastic paraplegias (HSPs) are occasionally included in hereditary ataxias owing to some overlaps of ataxia as part of the clinical presentations of HSPs.[1] In addition to sporadic and hereditary ataxias, various diseases may also present with ataxias, which include mitochondrial diseases, congenital diseases, metabolic diseases, autoimmune diseases, remote effects of malignancies, infectious diseases, and intoxications.

With recent remarkable advances in molecular genetics studies, many causative genes have been discovered in hereditary ataxias. Although these advances no doubt contribute to a better understanding of hereditary ataxias, we are now facing the difficulty in conducting comprehensive genetic tests to establish the molecular diagnosis of patients with hereditary ataxias, because they are costly.[2] Through the genetic tests of hereditary ataxias, we have learned that the molecular epidemiology of hereditary ataxias varies considerably among populations.[1] For example, while Friedreich's ataxia is the most common hereditary ataxia with autosomal recessive inheritance in European descent populations, we have never encountered a single case of Friedreich's ataxia in the Japanese population. In contrast, spinocerebellar ataxia type 3 (SAC3), also called Machado–Joseph disease (MJD), is the most common form of hereditary ataxia with autosomal dominant inheritance worldwide, despite the historical background that families with MJD were originally described in those originated from Azores, Portugal. Thus, neurologists need to consider not only the clinical presentations of individual hereditary ataxias but also the molecular epidemiology of hereditary ataxias to consider the algorithm of genetic tests for hereditary ataxias. The selection of appropriate diagnostic tests is important to save costs for genetic tests. To accomplish this, we need to have sufficient knowledge of the clinical presentations and epidemiology of individual diseases.

To facilitate diagnostic approaches, detailed epidemiological data of not only hereditary ataxias but also other diseases should be taken into consideration. Although many molecular epidemiological studies focusing on hereditary ataxias have been reported, only a limited number of comprehensive epidemiological studies focusing on diseases other than hereditary ataxias, including sporadic ataxias and other various forms of ataxias as described below, have been published to date.

As described in the paper published in this journal, Massuyama et al.[3] conducted a large-scale cross-sectional analysis of 1,332 patients with various forms of ataxias evaluated over 17 years at a single ataxia center, the Ataxia Unit at the Hospital São Paulo, in São Paulo, Brazil. They successfully established the diagnosis of 744 patients (55.9%), including 101 sporadic ataxia, 326 spinocerebellar ataxias (SCAs) (ataxias with autosomal dominant inheritance), 186 ARCAs (ataxias with autosomal recessive inheritance), 6 X-linked ataxias, and 51 HSPs. Among the hereditary ataxias with autosomal dominant inheritance, MJD/SCA3 is the most common type as similarly observed worldwide in previous studies.[1] Of interest, among the 17 patients with SCA6, 15 were Japanese descendants, raising the possibility that this relatively higher prevalence of SCA6 reflects the historical background that the city of São Paulo has been the main immigration destination of Japanese people. In contrast, the paper describes only a limited number of patients with SCA31 or those with dentatorubral-pallidoluysian atrophy (DRPLA), which are also relatively common types of hereditary ataxia with autosomal dominant inheritance in the Japanese population. Thus, we may need to further investigate the details of the Japanese immigration in relation to the original regions of the Japanese immigrants in Japan. Note that even in the Japanese population, the molecular epidemiology of hereditary

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ataxias shows considerably different regional differences.[4,5] In the ataxias with autosomal recessive inheritance identified in this study, Friedreich's ataxia was the most common type, as it has been observed similarly in European descent populations.

With regard to the sporadic ataxia group, the most common diagnosis was multiple system atrophy (MSA) ($n = 51$). MSA is a devastating neurological disease presenting with various combinations of autonomic symptoms, ataxia, and parkinsonism. The accurate diagnosis of MSA is often difficult, especially at the early stage. Special attention should be paid to the epidemiology of MSA since the relative frequencies of MSA-C (a subtype of MSA mainly presenting with ataxia) and MSA-P (a subtype mainly presenting with parkinsonism) differ between European descent populations and East Asian populations.[6,7] The relative frequencies of MSA-C and MSA-P in the Brazilian population would be helpful in the investigation of the epidemiology of MSA in Brazil. Since patients with MSA-P may not have been referred to the ataxia center, epidemiological investigation of MSA should be further broadened to include patients with MSA-P.

Importantly, the study by Massuyama et al. further identified patients with other ataxias, which include 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 ($n = 3$). Of note, there were 8 immune-mediated cerebellar ataxias, including the Sjogren syndrome ($n = 2$), as well as those with the neuronal antigens anti-GAD ($n = 4$), anti-Hu ($n = 1$), and anti-Yo ($n = 1$). These observations strongly emphasize the necessity to include various forms of ataxias in the differential diagnosis of ataxias in clinical practice. In particular, it should be emphasized that treatable diseases are included in this group.

As described by the authors, the diagnosis was not established in 588 (44.1%) of the 1,332 patients with various forms of ataxias. Thus, further investigations based on broad research disciplines are encouraged to better understand the diseases with ataxias. In the field of molecular genetics, investigations focusing on dynamic aspects of the human genome, including expanded tandem repeats, imprinting, *de novo* mutations, mosaicisms, and epigenetic changes, should be explored.[8–10] The development of highly effective therapies based on the elucidated disease mechanisms is the ultimate goal of these molecular genetics research studies.

Conflict of Interest

There is no conflict of interest to declare.

References

1 Ruano L, Melo C, Silva MC, Coutinho P. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. Neuroepidemiology 2014;42(03):174–183. Doi: 10.1159/000358801

2 da Graça FF, Peluzzo TM, Bonadia LC, et al. Diagnostic yield of whole exome sequencing for adults with ataxia: a Brazilian perspective. Cerebellum 2022;21(01):49–54. Doi: 10.1007/s12311-021-01268-1

3 Massuyama BK, Gama MTD, Silva TYT, Braga-Neto P, Pedroso JL, Barsottini OGP. Ataxias in Brazil: 17 years of experience in an ataxia center. Arq Neuropsiquiatr 2024;82(08):1–8. Doi: 10.1055/s-0044-1787800

4 Matsumura R, Futamura N, Ando N, Ueno S. Frequency of spinocerebellar ataxia mutations in the Kinki district of Japan. Acta Neurol Scand 2003;107(01):38–41. Doi: 10.1034/j.1600-0404.2003.01347.x

5 Mori M, Adachi Y, Kusumi M, Nakashima K. A genetic epidemiological study of spinocerebellar ataxias in Tottori prefecture, Japan. Neuroepidemiology 2001;20(02):144–149. Doi: 10.1159/000054775

6 Watanabe H, Saito Y, Terao S, et al. Progression and prognosis in multiple system atrophy: an analysis of 230 Japanese patients. Brain 2002;125(Pt 5):1070–1083. Doi: 10.1093/brain/awf117

7 Tsuji S, Onodera O, Goto J, Nishizawa M, Study Group on Ataxic Diseases. Sporadic ataxias in Japan–a population-based epidemiological study. Cerebellum 2008;7(02):189–197. Doi: 10.1007/s12311-008-0028-x

8 Ishiura H, Tsuji S. Advances in repeat expansion diseases and a new concept of repeat motif-phenotype correlation. Curr Opin Genet Dev 2020;65:176–185. Doi: 10.1016/j.gde.2020.05.029

9 Ishiura H, Shibata S, Yoshimura J, et al. Noncoding CGG repeat expansions in neuronal intranuclear inclusion disease, oculopharyngodistal myopathy and an overlapping disease. Nat Genet 2019;51(08):1222–1232. Doi: 10.1038/s41588-019-0458-z

10 Ishiura H, Doi K, Mitsui J, et al. Expansions of intronic TTTCA and TTTTA repeats in benign adult familial myoclonic epilepsy. Nat Genet 2018;50(04):581–590. Doi: 10.1038/s41588-018-0067-2