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https://doi.org/10.35839/repis.5.3.1014

Genetic clinical characterization of patients with hereditary ataxias in the state of Portuguesa-Venezuela

Caracterización clínica genética de pacientes con ataxias hereditarias en el estado de Portuguesa- Venezuela

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Abstract

Introduction: hereditary ataxias are neurodegenerative diseases that cause functional deterioration. As a consequence of their progressive nature, they lead to disability in affected individuals with severe psychological damage in their families. **Objective**: to characterize clinically and genetically the patients with hereditary ataxias in the Portuguese-Venezuela state in the period 2013-2015. **Methods**: an observational, descriptive cross-sectional study was carried out in patients with a diagnosis of hereditary ataxia. The universe consisted of 33 patients diagnosed in the study period, we worked with all of them. The individual and family health histories were reviewed. The data obtained were processed using the SPSS statistical program. **Results**: there was a predominance of the age group 25-29 years (18.18%) and the male sex (51.5%); as well as adult autosomal dominant spinocerebellar ataxias (SCA1 and SCA2) (82%). Stage 3 disease patients were the most prevalent (40%). The autosomal dominant type of inheritance predominated (69%) and the paternal inheritance path (63%). **Conclusions**: community genetics and genetic counseling contributed with therapeutic alternatives to improve the quality of life. In addition, the populations at risk were identified to outline preventive actions and reduce the recurrence of hereditary conditions.

Keyword: hereditary ataxias, disability, genetic counseling.

Resumen

Introducción: las ataxias hereditarias son enfermedades neurodegenerativas que provocan deterioro funcional. Como consecuencia de su carácter progresivo conllevan a la discapacidad en los individuos afectados con una severa afectación psicológica en sus familias. **Objetivo**: caracterizar clínico y genéticamente los pacientes con ataxias hereditarias en el estado Portuguesa- Venezuela en el periodo 2013-2015. **Métodos**: se realizó un estudio observacional, descriptivo de corte transversal en pacientes con diagnóstico de ataxia hereditaria. El universo estuvo constituido por 33 pacientes diagnosticados en el periodo de estudio, se trabajó con todos ellos. Se realizó la revisión de las historias de salud individual y familiar. Los datos obtenidos fueron procesados mediante programa estadístico SPSS. **Resultados**: existió predominio del grupo de edad de 25-29 años (18.18 %) y del sexo masculino (51.5%); así como de las ataxias espinocerebelosas autosómicas dominantes del adulto (SCA1 y la SCA2) (82 %). Los pacientes en etapa 3 de la enfermedad fueron los más predominantes (40 %). Predominó el tipo de herencia autosómica dominante (69 %) y la vía de herencia paterna (63 %). **Conclusiones**: la genética comunitaria y el asesoramiento genético contribuyeron con alternativas terapéuticas para mejorar la calidad de vida. Además, quedaron identificadas las poblaciones de riesgo para trazar acciones preventivas y reducir la recurrencia de las afecciones hereditarias.

Palabras clave: ataxias hereditarias, discapacidad, asesoramiento genético.

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Reception date: march 21, 2021

Approval date: may 30, 2021

Quote as: Castro-Montesino D, Iglesias-Rojas MB, Ramos-Fernández O, Rojas-Concepción AA. Caracterización clínica genética de pacientes con ataxias hereditarias en el estado de Portuguesa-Venezuela. Rev. Peru. Investig. Salud. [Internet]; 5(3): 207-211. Available from: http://revistas.unheval.edu.pe/index.php/repis/article/view/895

Introduction

Autosomal dominant spinocerebellar ataxias (ADCAs) constitute a clinically and genetically heterogeneous group of neurodegenerative diseases characterized by progressive ataxia variably associated with other neurological signs and caused by gradual degeneration of the cerebellum and brainstem. (1-5)

According to the age of onset of hereditary ataxias, these are usually classified into two large groups, those with early and late onset. Within the first, there are those that are inherited with an autosomal recessive inheritance pattern, associated or not with metabolic disorders. Recessive ataxias not associated with defined metabolic disorders are progressive and among them are Friedreich's ataxias, due to vitamin E deficiency, telangiectatic and other syndromes that present with DNA repair disorders, with oculomotor apraxia, autosomal recessive spastic and recessive myoclonic. (6-10)

Hereditary late-onset or adult ataxias are generally inherited in an autosomal dominant pattern of inheritance. These are characterized by the isolated or predominantly combined degeneration of the cerebellum, the spinal cord and their connecting pathways, which is why it is traditionally known as Spinocerebellar Ataxias (SCA, from the English Spinocerebellar Ataxia). Among the ataxias with an autosomal dominant inheritance pattern are ACS, Ataxic Syndromes, Episodic Ataxias and other Dominant Syndromes that occur with Ataxia. (7-12) The genetic heterogeneity of Dominant Autosomal Ataxias suggests that at least 30% of their molecular etiology remains to be identified. (11,13,15)

On some occasions, certain trinucleotides are repeated in a number higher than the normal range and this fact is associated with the presence of some generally neurological and / or neuromuscular pathology. This type of alteration is known as a dynamic mutation because it presents a series of characteristics that make it different from the classic Mendelian mutations that are static. (12) Ataxias SCA1, SCA2, SCA3, SCA6, SCA7, SCA17, dentato-rubro-luysian atrophy, spino-bulbar atrophy and Huntington's disease, are within the group of diseases caused by expansions of the

trinucleotide CAG, also called polyglutamine diseases because they all have one point in common: the expansion of a CAG triplet that codes for glutamine. (11-16)

Prevalence studies of autosomal dominant hereditary ataxias are rare internationally. However, it has been estimated that the most common subtype internationally is SCA3, which represents a little more than 30% of all autosomal dominant inherited ataxias. The other molecular forms with significant prevalence values are SCA2, SCA6, SCA7 and SCA8. (8,10,14,16,17)

Genetic counseling is the undirected communication process that the specialist maintains with a person in relation to the condition, evolution or transmission of a disease of genetic origin. The person requesting genetic counseling may be affected by the disease (testing) or be an apparently healthy relative of the affected (consultant). During the genetic counseling process, the professional must ensure that the patient and / or family are provided with the necessary information to: know and understand the diagnosis made, their prognosis and treatment, if any, the type of inheritance, and the risk of recurrence that implies, in addition to knowing the alternatives available to reduce or eliminate the risk of recurrence of the disease, choosing an appropriate strategy according to the existing risk, the wishes of the family and their ethical or religious convictions and adapting as best as possible to the new personal, family and socio-labor situation. (19,20)

In Venezuela, the prevalence of hereditary ataxias, the number of affected families and subjects at risk of becoming ill are unknown, with the completion of this research a significant accumulation of information will be provided that will contribute to the epidemiological and clinical characterization, to the understanding of the population genetics of these pathologies and the implementation of intervention strategies such as physical and cognitive rehabilitation and the establishment of molecular diagnosis. The Portuguese state has a significant number of families with a diagnosis of neurodegenerative diseases and hereditary ataxias distributed in nine municipalities of the state, with a lack of knowledge of the disease and the cause of the disability.

This research was developed with the objective of clinically and genetically characterizing patients with hereditary ataxias in the Portuguese-Venezuela state in the period 2013-2015.

Methods

An observational, descriptive cross-sectional study was carried out in patients with a diagnosis of hereditary ataxia in the Portuguese state of the Bolivarian Republic of Venezuela in the period 2013-2015. The universe consisted of 33 patients with a diagnosis of hereditary ataxia in the study period.

A classification was established based on the degree of validity of our patients. (Annex 1), as well as conducting some studies such as: neurological examination and clinical scale. (Appendix 2)

The SARA Scale (Scale for assessment and rating of ataxia) (Schmitz-Hübsch et al, 2006) was applied for the estimation of cerebellar damage, which allowed an evaluation of the alterations, including the following aspects: walking, standing (stay erect), sitting, language disorders, tracking, alternate hand movements, heel-knee test.

The variables studied were: sex, age, type of ataxia, clinical stages of the disease and type of inheritance.

The data obtained were deposited in a database prepared for this purpose and processed in the statistical package Statistical Package for the Social Sciences (SPSS) version 21.0. To describe the behavior of the variables, it was analyzed in a univariate way using absolute frequencies and percentages. The research was approved by the scientific council and ethics committee. The ethical principles of the Helsinki declaration were followed.

Results

There was a predominance of the age group 25-29 years (18.18%) and males (51.5%). (Table 1)

A predominance of adult autosomal dominant spinocerebellar ataxias was found (82%), followed by Friedrich's ataxias (12%) and sporadic ataxias (6%).

It was evidenced that 40% of the patients in the study were found in stage 3 of the disease, followed by stage 2 (33%) and stage 1 (27%).

A predominance of the autosomal dominant type of inheritance (69%) was found, followed by the autosomal recessive (19%). In 12% the type of inheritance was not specified.

Those who exhibited a paternal inheritance were superior (63%), followed by those in which both parents were carriers (25%) and lastly those who presented a path of maternal inheritance (12%).

Discussion

The Portuguese state ranks third in the country with the highest prevalence of physical-motor and mixed disability due to genetic diseases such as hereditary ataxias. In the first psychopedagogical and social clinical-genetic study, 18 families with a diagnosis of

Table 1. Distribution according to age and sex of patients with hereditary ataxia in the Portuguese-Venezuela state in the period 2013-2015

Age Group (Years)	Total of patients		Sex			
			Female		Male	
	No.	%	No.	%	No.	%
1-Abr	1	3.03	1	3.03	0	0
5-Set	1	3.03	1	3.03	0	0
Oct-14	3	9.09	0	0	3	9.09
15-19	3	9.09	2	6.06	1	3.03
20-24	4	12.12	3	9.09	1	3.03
25-29	6	18.18	2	6.06	4	12.12
30-34	3	9.09	2	6.06	1	3.03
35-39	1	3.03	0	0	1	3.03
40-44	4	12.12	1	3.03	3	9.09
45-49	3	9.09	1	3.03	2	6.06
50-54	2	6.06	1	3.03	1	3.03
55-59	1	3.03	1	3.03	0	0
60 years and over	1	3.03	1	3.03	0	0
Total	**33**	**100**	**16**	**48.5**	**17**	**51.5**

Source: Individual clinical history of genetics.

ACS were detected. These families are distributed in 9 municipalities of the state: Unda, Guanare, Ospino, Guanarito, Papelón, Araure, Páez, Esteller, Turén.

Sixteen families have been treated, 6 new cases have been detected, 14 deaths and 33 patients have been evaluated in consultation from the clinical-genetic point of view by multidisciplinary teams where other specialists such as neurologist, defectologist, physiatrist and clinical geneticist participate according to availability of human resources in the different health areas.

In the description of sociodemographic variables such as age and sex, no differences were found in relation to the affection and sex, so there is no predominance of one over the other but rather affects indistinctly. In relation to age, the highest percentage of patients is in the range of 20-59 years, which is in relation to the ages of onset of the first symptoms of the disease and the phenomenon of anticipation that characterizes the disease. Similar results are observed in other studies carried out in Cuba (13,17).

Of the total number of patients evaluated, adult autosomal dominant spinocerebellar ataxias, of the type: SCAs 2, 7, according to clinical characteristics and neurological signs, are the most frequent in the present study.

These sSCAs are within the group of expansions due to an increase in CAG trinucleotides, also called polyglutamine disorders. From the epidemiological point of view, they are the most frequent in the American continent, demographic studies indicate families with type 3 SCAs in Brazil, type 2 SCAs in Cuba and type 7 SCAs in Venezuela, as well as Friedreich's ataxia is the most frequent inherited ataxia in the United States. (3, 4, 7,11-13)

Knowing the family genetic history through the genealogical tree as the main professional tool in the field of medical genetics is the first step for the identification of genetic risk, which in terms of community genetics is aimed at the search for predisposition for diseases of Mendelian origin and reproductive genetic risk. The introduction of clinical genetics services in the community; Genetic counseling makes it possible to carry out strategies that are aimed at reducing the recurrence of disabilities due to these causes, offering the population adequate information on their risks, about planning their offspring to improve the quality of life and education in general of the populations. vulnerable. (18-20)

The main objective of the applications of genetics to public health is to reduce the impact of genetic diseases on the health and well-being of individuals through prevention strategies, as well as to reduce their frequency, contributing to the modification of the gene pool of our species, helping passively by acting on individual families or actively through health policies that contribute to improving the quality of life of the population in communities where there is a higher prevalence. (19,20)

Taking into account that in the autosomal dominant hereditary ataxias of the adult there is a phenomenon of anticipation, it is very important to draw up prevention and counseling strategies for these families, explaining the possibility that these

descendants are pre symptomatic people.

Neurorehabilitation and vitamin therapy in high doses make it possible to improve the quality of life of people with spinocerebellar ataxias, improving the cognitive state and the symptoms in a general way. Studies carried out in Cuba show benefits of physical exercise in patients diagnosed with hereditary ataxias in light stages. (17-20)

A predominance of the age group 25-29 years and male was found; adult autosomal dominant spinocerebellar ataxias were the most frequent. Most of the patients were in stage 3 of the disease. The autosomal dominant type of inheritance and paternal inheritance predominated.

Conflicts of interests

The authors declare that they don't have conflicts of interests.

Authors' contributions

DCM participated in the conception and design of the research and data collection. DCM, MBIR y ORF participated in the statistical processing of the data. DCM, MBIR y AARC were in charge of writing the article. All authors reviewed and approved the manuscript and its final version.

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