https://doi.org/10.1590/0004-282X20180001

Otoneurological findings prevalent in hereditary ataxias

Alterações otoneurológicas prevalentes nas ataxias hereditárias

Bianca Simone Zeigelboim[1], Hélio A. G. Teive[2], Geslaine Janaína Barbosa Santos[3], Maria Izabel Rodrigues Severiano[3], Vinicius Ribas Fonseca[1], João Henrique Faryniuk[1], Jair Mendes Marques[1]

ABSTRACT

Objective: To describe and compare the vestibular findings most evident among the hereditary ataxias, as well as correlate their clinical features with the nervous structures affected in this disease. **Methods:** Seventy-five patients were evaluated and underwent a case history, otorhinolaryngological and vestibular assessments. **Results:** Clinically, the patients commonly had symptoms of gait disturbances (67.1%), dizziness (47.3%), dysarthria (46%) and dysphagia (36.8%). In vestibular testing, alterations were predominantly evident in caloric testing (79%), testing for saccadic dysmetria (51%) and rotational chair testing (47%). The presence of alterations occurred in 87% of these patients. A majority of the alterations were from central vestibular dysfunction (69.3%). **Conclusion:** This underscores the importance of the contribution of topodiagnostic labyrinthine evaluations for neurodegenerative diseases as, in most cases, the initial symptoms are otoneurological; and these evaluations should also be included in the selection of procedures to be performed in clinical and therapeutic monitoring.

Keywords: spinocerebellar ataxias; vestibular diseases; chronic disease.

RESUMO

Objetivo: Descrever e comparar os achados vestibulares mais evidentes entre a ataxia hereditária, bem como correlacionar seus aspectos clínicos com o estudo das estruturas nervosas afetadas nesta doença. **Métodos:** 75 pacientes foram avaliados e submetidos aos seguintes procedimentos: anamnese, avaliação otorrinolaringológica e vestibular. **Resultados:** Clinicamente, os pacientes apresentaram sintomas de distúrbios da marcha (67,1%), tonturas (47,3%), disartria (46%) e disfagia (36,8%). No teste vestibular, as alterações foram predominantemente evidentes no teste calórico (79%), dismetria sacádicas (51%) e no teste rotatório (47%). A presença de alterações ocorreu em 87% dos pacientes. A maioria das alterações observadas foram da disfunção vestibular central (69,3%). **Conclusão:** O estudo ressalta a importância da contribuição da avaliação labiríntica no topodiagnóstico para doenças neurodegenerativas, uma vez que, na maioria dos casos, os sintomas iniciais são otoneurológicos, e essas avaliações também devem ser incluídas na seleção de procedimentos a serem realizados no monitoramento clínico e terapêutico.

Palavras-chave: ataxias espinocerebelares; doenças vestibulares; doença crônica.

Hereditary ataxias are a heterogeneous group of neurodegenerative diseases that are characterized by the presence of progressive cerebellar ataxia and have initial clinical manifestations such as deterioration of balance and coordination, as well as ocular disorders[1,2,3,4]. Based on genetic inheritance, ataxias can be divided into: 1) autosomal recessive cerebellar ataxias (ARCAs); 2) autosomal dominant cerebellar ataxias, or dominant spinocerebellar ataxias (SCAs); 3) X-linked hereditary ataxia (related to the X chromosome); and 4) mitochondrial ataxias[5].

Within the group of ARCAs, we highlight Friedreich's ataxia. It is a rare neurodegenerative disease, progressive in nature, and has autosomal recessive early onset in most cases[6,7,8].

The mutation responsible for the disease is located on chromosome nine, where there is a GAA trinucleotide expansion in the X25 gene. The affected gene has the function of encoding the mitochondrial protein, frataxin, that is involved in iron metabolism[7,8,9]. The deficit of this protein causes the accumulation of iron within the mitochondria disturbing the mitochondrial respiratory chain and increasing

[1]Universidade Tuiuti do Paraná, Departamento de Otoneurologia, Curitiba PR, Brasil;

[2]Universidade Federal do Paraná, Hospital de Clínicas, Serviço de Neurologia, Curitiba, PR, Brasil;

[3]Instituto Federal de Educação, Ciência e Tecnologia do Paraná, Curitiba PR, Brasil.

Correspondence: Bianca Simone Zeigelboim; Departamento de Otoneurologia da Universidade Tuiuti do Paraná; R. Gutenberg, 99 / 9º andar; 80420-030 Curitiba PR, Brasil; E-mail: bianca cwb@yahoo.com.br

Conflict of interest: There is no conflict of interest to declare.

Received 27 July 2017; Received in final form 15 November 2017; Accepted 06 December 2017.

oxidative stress[6,9,10]. The first symptoms are usually observed in childhood or the early teen years; however, in some cases the diagnosis can be made before two or after 20 years of age. The main features of the disease are: ataxia (impaired coordination) that initially affects the lower limbs and then the upper, absence of tendon reflexes and weakness in the lower limbs, dysarthria, loss of distal deep sensation, and bilateral Babinski sign. Nerve conduction studies show sensory axonal neuropathy[9,11]. Other features associated with this medical condition are: nystagmus, optic atrophy, hearing loss, atrophy in the hands and distal lower limbs, scoliosis, pes cavus, and hammer toes[6,11].

Within the group of SCAs, we highlight types 2, 3, 6, 7 and 10, which are of interest in this study. The most common clinical symptoms in SCAs present as gait and appendage ataxia (dysmetria, diadochokinesia in limbs, intentional tremors), dysarthria, nystagmus, ophthalmoplegia, dysphagia, hearing loss (in some patients), pyramidal signs, lower motor neuron syndrome, cognitive dysfunction, epilepsy, visual disturbances (pigmentary retinopathy), peripheral neuropathy, dementia and movement disorders (including parkinsonism, dystonia, myoclonus and chorea)[1,12].

The SCA types 2, 3, 6, and 7 are related to unstable CAG repeat expansions in the respective gene, and are classified as polyglutamine disorders[1,12,13,14]. The SCA10 is caused by a repeat expansion of an ATTCT pentanucleotide, in the intron 9 of the gene located in the chromosome 22q13.3.

Different clinical and neuropathological studies in hereditary ataxias have shown that each specific genetic entity has a constellation of signs and symptoms that are related to the duration of the disease and the size of trinucleotide repeat expansion. Thus, the combination of molecular genetic data and clinical signs provide useful information serving as the basis for the genotypic and phenotypic classification of ataxias[15].

Hereditary ataxias are part of a list of diseases that, by their manifestations and impairment areas, can lead to vestibular disorders, and the labyrinthine examination is an important tool in the confirmation of vestibular disorders and their relationship with the central nervous system[16].

The aim of this study was to describe and compare the vestibular findings most evident among the hereditary ataxias, as well as correlate their clinical features with the nervous structures affected in this disease.

METHODS

The research protocol was approved by the Ethics Committee on Research Involving Human Subjects (registration number CEP nº. 832.502/2014) following the Brazil Platform. All examinations were performed after formal consent forms were obtained from all participants.

The study had a retrospective cross-sectional design. Seventy-five patients with ataxia were evaluated, 56 with SCAs (26 females and 30 males) and 19 with ARCAs (eight females and 11 males). Among them, 37 patients had a genetically-proven diagnosis of SCAs, and six of Friedreich's ataxia. The diagnosis of ataxia was made by analysis of clinical and genetic tests using the polymerase chain reaction[17,18]. This reaction is based on the fact that the oligonucleotides (primers) hybridize specifically to a DNA template strand enabling the production of multiple copies of specific DNA sequences[19].

The ages of the SCA patients ranged from 18 to 70 years (mean, 42.7 ± 12.4 years). The duration of the disease ranged from one to 18 years (mean, 8.4 ± 4.1 years) and the ages of the ARCA patients ranged from six to 63 (mean, 36.7 ± 14.3 years). The duration of the disease ranged from three to 38 years (mean, 16.2 ± 9.2 years), as shown in Tables 1 and 2.

Included in the survey were patients without otoscopic alterations, and excluded were patients with musculoskeletal changes that prevented the examination.

The patients were subjected to the following procedures:

1) Anamnesis: a questionnaire was given with an emphasis on otoneurological signs and symptoms.

2) Otorhinolaryngological assessment: this was performed to rule out any alteration that could affect the test.

3) Vestibular assessment: evaluation of the vestibular function comprises many labyrinthine function and ocular tests. The first part of our patients' evaluation was clinical and consisted of a systematic search for spontaneous, gaze, and positional nystagmus. The second part consisted of interpretation of the vectoeletronystagmography test result, which is the objective register of the variations in the corneoretinal potentials, captured by sensitive electrodes. The vectoeletronystagmography test comprises calibration of ocular movements, search for spontaneous and gaze nystagmus, the oscillatory tracking test, an optokinetic nystagmus search, and rotatory and caloric tests. We performed the vectoeletronystagmography using three-channel equipment (Berger Eletromedicina, model VN316, made in São Paulo, Brazil), a rotating chair (Ferrante, model COD 14200, made in São Paulo, Brazil), a visual stimulator (Neurograff Eletromedicina, model EV VEC, São Paulo, Brazil), and an air caloric stimulator (Neurograff Eletromedicina, model NGR 05, São Paulo, Brazil).

We compared our results with normal standards, obtained from epidemiological studies in the Brazilian population[20,21]. The criteria used to analyze each test, as well as to distinguish central from peripheral vestibulopathy, are shown in Table 3.

Statistical analysis

We applied the two-proportion z-test to check the most evident symptoms, check which tests presented the most alterations and compare the results of the vestibular examination (analyzing normal and abnormal results) in SCAs and ARCAs and compare them with each other.

Table 1. Summary of patient demographics and genetic diagnoses in SCAs.

Patient	Age/sex (years)	SCA type	Disease duration (years)	Chromosomal locus of abnormality	Gene affected	Mutation type	Protein affected	SARA
1	42/M	SCA3	12	14q32.1	*ATXN3*	CAG	Ataxin-3	4
2	48/F	SCA3	15	14q32.1	*ATXN3*	CAG	Ataxin-3	10
3	43/M	SCA3	12	14q32.1	*ATXN3*	CAG	Ataxin-3	4.5
4	41/M	SCA3	8	14q32.1	*ATXN3*	CAG	Ataxin-3	10.5
5	48/F	SCA3	10	14q32.1	*ATXN3*	CAG	Ataxin-3	10.5
6	53/M	SCA3	13	14q32.1	*ATXN3*	CAG	Ataxin-3	13
7	50/F	SCA3	8	14q32.1	*ATXN3*	CAG	Ataxin-3	9.5
8	30/F	SCA3	9	14q32.1	*ATXN3*	CAG	Ataxin-3	11
9	42/M	SCA3	10	14q32.1	*ATXN3*	CAG	Ataxin-3	7.5
10	45/M	SCA3	15	14q32.1	*ATXN3*	CAG	Ataxin-3	11
11	51/M	SCA3	7	14q32.1	*ATXN3*	CAG	Ataxin-3	1.5
12	45/M	SCA3	3	14q32.1	*ATXN3*	CAG	Ataxin-3	25.5
13	32/F	SCA3	5	14q32.1	*ATXN3*	CAG	Ataxin-3	10
14	46/F	SCA3	11	14q32.1	*ATXN3*	CAG	Ataxin-3	7
15	49/M	SCA2	11	12q24.1	*ATXN2*	CAG	Ataxin-2	33
16	42/F	SCA2	8	12q24.1	*ATXN2*	CAG	Ataxin-2	21.5
17	54/F	SCA2	11	12q24.1	*ATXN2*	CAG	Ataxin-2	28
18	38/M	SCA2	8	12q24.1	*ATXN2*	CAG	Ataxin-2	4.0
19	41/M	SCA2	12	12q24.1	*ATXN2*	CAG	Ataxin-2	4.5
20	36/M	SCA2	3	12q24.1	*ATXN2*	CAG	Ataxin-2	21
21	18/M	SCA2	2	12q24.1	*ATXN2*	CAG	Ataxin-2	18
22	44/F	SCA2	3	12q24.1	*ATXN2*	CAG	Ataxin-2	21
23	30/F	SCA2	10	12q24.1	*ATXN2*	CAG	Ataxin-2	4
24	42/M	SCA2	12	12q24.1	*ATXN2*	CAG	Ataxin-2	9.5
25	59/M	SCA6	13	19q13.1	*CACNA1A*	CAG	CACNA1A	17.5
26	57/F	SCA6	5	19q13.1	*CACNA1A*	CAG	CACNA1A	4
27	49/M	SCA7	13	3p14.1	*ATXN7*	CAG	Ataxin-7	35
28	47/F	SCA7	10	3p14.1	*ATXN7*	CAG	Ataxin-7	16
29	52/F	SCA10	16	22q13.3	*ATXN10*	ATTCT	Ataxin-10	7
30	30/M	SCA10	4	22q13.3	*ATXN10*	ATTCT	Ataxin-10	9
31	37/F	SCA10	3	22q13.3	*ATXN10*	ATTCT	Ataxin-10	7
32	49/F	SCA10	6	22q13.3	*ATXN10*	ATTCT	Ataxin-10	16
33	46/M	SCA10	10	22q13.3	*ATXN10*	ATTCT	Ataxin-10	13
34	27/F	SCA10	3	22q13.3	*ATXN10*	ATTCT	Ataxin-10	14
35	70/M	SCA10	13	22q13.3	*ATXN10*	ATTCT	Ataxin-10	4
36	54/M	SCA10	11	22q13.3	*ATXN10*	ATTCT	Ataxin-10	10
37	56/F	SCA10	12	22q13.3	*ATXN10*	ATTCT	Ataxin-10	10
38	63/F	Und.	10	-	-	-	-	7
39	48/M	Und:	18	-	-	-	-	16
40	58/F	Und.	10	-	-	-	-	4.5
41	35/F	Und.	5	-	-	-	-	9
42	45/F	Und.	9	-	-	-	-	9
43	24/M	Und.	2	-	-	-	-	21
44	27/M	Und.	7	-	-	-	-	7
45	20/M	Und.	1	-	-	-	-	9.5
46	32/M	Und.	5	-	-	-	-	18.5
47	22/M	Und.	8	-	-	-	-	9.5
48	22/M	Und.	7	-	-	-	-	16
49	62/M	Und.	3	-	-	-	-	8
50	66/M	Und.	12	-	-	-	-	9.5
51	18/F	Und.	4	-	-	-	-	16
52	23/M	Und.	1	-	-	-	-	10.5
53	37/F	Und.	9	-	-	-	-	10.5
54	48/F	Und.	8	-	-	-	-	11
55	48/F	Und.	8	-	-	-	-	25
56	51/F	Und.	7	-	-	-	-	25.5

SCAs: dominant spinocerebellar ataxias; SCA: spinocerebellar ataxia; Und.: undetermined; M: male; F: female; SARA: scale for the assessment and rating of ataxia.

Table 2. Summary of patient demographics and genetic diagnoses in ARCAs.

Patient	Age/sex (years)	ARCA type	Disease duration (years)	Chromosomal locus of abnormality	Gene affected	Mutation type	Protein affected	SARA
1	43/M	FA	25	9 q13-q21.1	*X25*	GAA	Frataxin	21
2	41/M	FA	7	9 q13-q21.1	*X25*	GAA	Frataxin	10
3	30/F	FA	18	9 q13-q21.1	*X25*	GAA	Frataxin	8
4	24/M	FA	8	9 q13-q21.1	*X25*	GAA	Frataxin	10.5
5	29/M	FA	13	9 q13-q21.1	*X25*	GAA	Frataxin	14
6	17/M	FA	3	9 q13-q21.1	*X25*	GAA	Frataxin	13
7	63/F	Und.	38	-	-	-	-	7
8	06/F	Und.	6	-	-	-	-	19
9	37/F	Und.	19	-	-	-	-	28
10	41/F	Und.	20	-	-	-	-	11
11	27/F	Und.	12	-	-	-	-	1.5
12	25/F	Und.	12	-	-	-	-	25.5
13	55/F	Und.	30	-	-	-	-	7
14	44/M	Und.	10	-	-	-	-	3.5
15	55/M	Und.	12	-	-	-	-	28
16	37/M	Und.	17	-	-	-	-	4.0
17	51/M	Und.	30	-	-	-	-	9.5
18	27/M	Und.	10	-	-	-	-	16
19	46/M	Und.	18	-	-	-	-	10

ARCA: autosomal recessive cerebellar ataxia; Und.: undetermined; M: male; F: female; FA: Friedreich's ataxia; SARA: scale for the assessment and rating of ataxia.

Table 3. Normal standards and criteria used to analyze the vestibular tests and distinguish central from peripheral[20,21].

Variable	Normal Vestibular Exam	Peripheral Vestibular Exam	Central Vestibular Exam
Position nystagmus (Brandt & Daroff's maneuver)	Absent	Present (rotatory, horizontal rotatory, and oblique) with latency, paroxysm, weariness, and vertigo	Present (vertical inferior, superior, rotatory, horizontal rotatory, and oblique), without latency, paroxysm, weariness, and vertigo
Calibration of the ocular movements	Regular	Regular	Irregular (alterations in latency, accuracy, and velocity of the saccadic movements)
Spontaneous nystagmus	Present (< 7degrees/sec) with closed eyes; absent with open eyes.	Present (> 7 degrees/sec) with closed eyes; absent with open eyes.	Present with open eyes (vertical inferior, superior, rotatory, horizontal rotatory, oblique, cyclic, dissociated, and convergence-retraction)
Gaze nystagmus	Absent	Absent	Present, unidirectional, bidirectional, or mixed; presents a variety of nystagmus types
Oscillatory track	Types I and II	Type III	Type IV (pathognomonic); alterations of morphology and gain
Optokinetic nystagmus	Symmetrical, < 20 degrees/sec	Asymmetrical, > 20 degrees/sec, having superimposed spontaneous nystagmus with open eyes that justifies this alteration	Asymmetrical, > 20 degrees/sec, absent and reduced
Rotation test	> 33%, after stimulation of the lateral and superior semicircular ducts	> 33%, after stimulation of the lateral and superior semicircular ducts	> 33%, after stimulation of the lateral and superior semicircular ducts and absence of induced oblique nystagmus
Air caloric test	Absolute value: between 2 and 24 degrees/sec Relative values: Labyrinth preponderance < 41% Nystagmus directional preponderance < 36%	Absolute value: < 2 degrees/sec (hyporeflexia), > 24 degrees/sec (hyperreflexia) and areflexia Relative values: Labyrinth preponderance > 41% Nystagmus directional preponderance > 36% (Jongkees formula)	Absolute value: < 2 degrees/sec (hyporeflexia), > 24 degrees/sec (hyperreflexia) and areflexia Relative values: Labyrinth preponderance >41% Nystagmus directional preponderance > 36% (Jongkees formula). Different nystagmus types may be observed: dissociated, inverted, perverted, and absence of the fast component of the nystagmus
Inhibiting effect of ocular fixation	Present	Present	Absent

We used the chi-squared test for SCAs and Fisher's exact test for ARCAs, to compare the results of the vestibular examination (analyzing the normal and altered results with gender as the variable). A value of 0.05 or 5% was established as the rejection level for the null hypothesis.

RESULTS

The most frequent complaints in the anamnesis were: gait imbalance (71.9% for SCAs and 52.6% for ARCAs), dysarthria (49.1% for SCAs and 36.8% for ARCAs), dizziness (43.8% for SCAs and 57.8% for ARCAs) and dysphagia (36.8% for both types of hereditary ataxia). It was found that headache was only mentioned by patients with an ARCA (42.1%), as shown in Table 4.

In the application of the two-proportion z-test, it was shown that there was no significant difference in the proportions of patients in both hereditary ataxias for the most common symptoms: gait imbalance (p = 0.1253), dysarthria (p = 0.3546), dizziness (p = 0.2933) and dysphagia (p = 1.0000). But the same test revealed that gait imbalance occurred in a higher proportion of cases in relation to the other symptoms, showing a statistical significance (p = 0.0142*).

The frequency of abnormal findings in the vestibular evaluation in both types of hereditary ataxias are shown in Table 5. It can be observed in the total values that bilateral vestibular hyporeflexia and saccadic dysmetria were more prevalent for SCAs at 73.2% and 62.5% respectively, while the frequency for ARCAs was 47.3% and 15.7% respectively. There was no post-rotatory nystagmus in either of the hereditary ataxias. However, multiple semi-spontaneous nystagmus and asymmetrical optokinetic nystagmus were found at 50% and 29%, respectively, in the last two tests for SCAs, while for the ARCAs there was a frequency of 36.8% in each of these tests. For ARCAs, spontaneous nystagmus with open eyes and bilateral vestibular hyperreflexia showed an alteration in 21% of patients.

The application of the two-proportion z-test revealed a significant difference between the proportions of patients with bilateral vestibular hyporeflexia and absence of post-rotatory nystagmus for the dominant SCAs total (p = 0.0138*) and ARCAs total (p = 0.0431*). Comparing the patients in both SCA total and ARCA total groups, the difference was significant only for saccadic dysmetria (p = 0.0009*).

Table 4. Symptoms in 75 patients with SCAs and ARCAs.

Symptoms	SCAs		ARCAs	
	No. patients	Frequency (%)	No. patients	Frequency (%)
Gait imbalance	41	71.9	10	52.6
Dysarthria	28	49.1	7	36.8
Dizziness	25	43.8	11	57.8
Dysphagia	21	36.8	7	36.8
Dysphonia	19	33.3	-	-
Hearing Loss	18	31.5	3	15.7
Headaches	14	24.5	8	42.1
Falling	14	24.5	6	31.5
Tingling in extremities	14	24.5	3	15.7
Diplopia	13	22.8	6	31.5
Tinnitus	13	22.8	-	-
Depression	12	21.0	4	21.0
Anxiety	11	19.2	4	21.0
Pain, radiated to shoulder, arm	10	17.5	5	26.3
Double vision	10	17.5	-	-
Tremors	9	15.7	6	31.5
Pain, difficulty in neck movement	9	15.7	4	21.0
Insomnia	8	14.0	1	5.2
Fatigue	8	14.0	5	26.3
Migraine	5	8.7	-	-
Taste alteration	-	-	1	5.2
Olfactory alteration	-	-	1	5.2
Cracking neck	-	-	3	15.7

SCAs: dominant spinocerebellar ataxias; ARCAs: autosomal recessive cerebellar ataxias; n: patients; %: frequency

The frequency of the vestibular test results in both hereditary ataxias, highlights the central vestibular dysfunction in all ataxias, as shown in Table 6.

The application of the two-proportion z-test showed a significant difference between the proportions of altered and normal results in SCAs total (p = 0.0000*) and ARCAs total (p = 0.0000*).

Regarding gender, the vestibular examination for SCAs showed alterations in males in 90% of cases and in females in 81% of cases. In the ARCAs, this alteration occurred in 83.4% of males and 100% of females, as indicated in Table 7.

The application of the chi-squared test showed that there was no significant relationship between altered and normal examinations in males and females (p = 0.5141) for SCAs, and the application of Fisher's exact test showed the same kind of result for ARCAs (p = 0.3860). Comparing results of altered and normal exams (both sexes) for SCA and ARCA groups resulted in no statistical significance (p = 0.5723).

Table 5. Frequency of abnormal findings in the vestibular evaluation in patients with SCAs and ARCAs.

Altered results	SCAs														ARCAs					
	SCA 2		SCA 3		SCA 6		SCA 7		SCA 10		Und.		SCAsT		FA		Und.		ARCAT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Bilateral labyrinthine hyporeflexia	5	50.0	13	92.8	2	100.0	2	100.0	5	55.5	14	73.6	41	73.2	3	50.0	6	46.1	9	47.3
Saccadic dysmetria	7	70.0	9	64.2	1	50.0	1	50.0	6	66.6	11	57.8	35	62.5	2	33.4	1	7.6	3	15.7
Rotational nystagmus absent	5	50.0	9	64.2	1	50.0	2	100.0	2	22.2	9	47.3	28	50.0	3	50.0	4	30.7	7	36.8
Multiple gaze nystagmus	-	0.0	4	28.5	1	50.0	1	50.0	5	55.5	5	26.3	16	29.0	4	67.0	3	23.0	7	36.8
Optokinetic asymmetrical nystagmus	2	20.0	8	57.1	-	0.0	2	100.0	2	22.2	2	10.5	16	29.0	3	50.0	4	30.7	7	36.8
Bidirectional gaze nystagmus	-	0.0	2	14.2	-	0.0	-	0.0	1	11.1	3	15.7	6	11.0	-	-	-	-	-	-
Positional nystagmus	1	10.0	-	0.0	1	50.0	-	0.0	1	11.1	2	10.5	5	9.0	-	-	-	-	-	-
Unidirectional gaze nystagmus	2	20.0	1	7.1	1	50.0	-	0.0	-	0.0	-	0.0	4	7.2	-	-	-	-	-	-
Unilateral labyrinthine hyporeflexia	1	10.0	-	0.0	-	0.0	-	0.0	-	0.0	3	15.7	4	7.2	-	-	-	-	-	-
Spontaneous nystagmus with open eyes	-	0.0	1	7.1	1	50.0	-	0.0	-	0.0	1	5.2	3	5.4	2	33.4	2	15.3	4	21.0
Unilateral labyrinthine hyperreflexia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	16.7	-	-	1	5.2
Bilateral labyrinthine hyperreflexia	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	4	30.7	4	21.0

SCAs: dominant spinocerebellar ataxias; Und: undetermined; SCAsT: dominant spinocerebellar ataxias total; FA: Friedreich's ataxia; ARCAs: autosomal recessive cerebellar ataxias; ARCAT: autosomal recessive cerebellar ataxia total; n: patients; %: frequency.

Table 6. Frequency of the vestibular exam results in SCAs and ARCAs.

Vestibular exam	SCAs														ARCAs					
	SCA 2		SCA 3		SCA 6		SCA 7		SCA 10		Und.		SCAsT		FA		Und.		ARCAT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Central vestibular dysfunction	6	60.0	11	78.5	2	100.0	2	100.0	6	66.7	14	73.7	41	73.2	4	66.6	7	53.8	11	57.9
Peripheral vestibular dysfunction	1	10.0	3	21.5	-	0.0	-	0.0	-	0.0	3	15.8	7	12.5	2	33.4	4	30.8	6	31.6
Normal vestibular exam	3	30.0	-	0.0	-	0.0	-	0.0	3	33.3	2	10.5	8	14.3	-	-	2	15.4	2	10.5
Total	10	100.0	14	100.0	2	100.0	2	100.0	9	100.0	19	100.0	56	100.0	6	100.0	13	100.0	19	100.0

SCAs: dominant spinocerebellar ataxias; Und: undetermined; SCAsT: dominant spinocerebellar ataxias total; ARCAs: autosomal recessive cerebellar ataxias; FA: Friedreich's ataxia; ARCAT: autosomal recessive cerebellar ataxia total; n: patients; %: frequency

Table 7. Distribution of patients with SCAs and ARCAs according to the results of the vestibular examination and gender.

Exam result	SCAs						ARCAs					
	Male		Female		Total		Male		Female		Total	
	n	%	n	%	n	%	n	%	n	%	n	%
Abnormal	27	90.0	21	81.0	48	85.7	10	83.4	7	100.0	17	89.5
Normal	3	10.0	5	19.0	8	14.3	2	16.6	-	-	2	10.5
Total	30	100.0	26	100.0	56	100.0	12	100.0	7	100.0	19	100.0

SCAs: dominant spinocerebellar ataxias; ARCAs: autosomal recessive cerebellar ataxias; n: patients; %: frequency

DISCUSSION

The symptoms most commonly reported by patients in both types of hereditary ataxia in the multiplicity of its clinical forms have been observed by different authors. Among the most common manifestations that may arise during the course of the disease were gait imbalance, dysarthria, dizziness and dysphagia[1,12]. Nacamagoe et al.[22] reported that vestibular dysfunction in combination with cerebellar atrophy could contribute significantly to the onset of gait instability, which was part of the initial symptomatology of ataxias.

Houssay[23] observed in SCA patients that the medial longitudinal fasciculus consisted largely of fibers derived from the vestibular nuclei and was involved in reflexes that allowed the eye to adjust to head movements. Information on the position of the head reach the medial longitudinal fasciculus through its connections with the vestibular nuclei. Before that, the author stated that the medial longitudinal fasciculus fibers terminate in the nuclei of oculomotor nerves III, IV and VI, paired with cranial nerves on the same and opposite sides, which explained the appearance of nystagmus in vestibular symptomatology.

In patients with Friedreich's ataxia, Oppenheimer[24] observed that the dentate nucleus displayed a moderate loss of neurons and the middle and superior cerebellar peduncles showed reductions in size. Furthermore, a loss of Purkinje cells in the cerebellar vermis and upper neurons in the corresponding portion of the inferior olivary nucleus was verified. The dentate nucleus usually had a severe cell loss. The vestibular and auditory systems were also affected by increased gliosis, especially at the level of the medial vestibular, cochlear and superior olivary nuclei. In addition, the author stated that the nuclei of cranial nerves VII, X and XII also showed a reduction in cell numbers, resulting in weakness of the face muscles, dysarthria and dysphagia. The globus pallidus and subthalamic nuclei were also affected; however, the striatum, thalamus and substantia nigra were spared. The cerebellar cortex was usually unchanged.

Regarding the vestibular examination, the alteration with the highest prevalence in both hereditary ataxias was bilateral vestibular hypofunction with 73.2% in SCAs and 47.3% in ARCAs. Saccadic dysmetria and a lack of response in the rotational test (62.5% and 50%) were the other most common alterations observed for SCAs. For ARCAs, rotary, optokinetic and semi-spontaneous nystagmus were the other most common alterations, present in 36.8% of patients. It is noteworthy that several alterations were observed in the various tests that make up the inner ear examination in both types of hereditary ataxias; the ones mentioned above were those that were most prevalent.

Although it is known that oculomotor abnormalities in patients with cerebellar dysfunction exist, it is also known that the cerebellum influences the maintenance of the eccentric portion of the eye, responsible for the smooth pursuit in eye movements, as well as the modulation in amplitude of saccades and visual suppression of caloric nystagmus[1].

The most common alterations in other studies[16,25] were the presence of positional nystagmus, irregular eye movement calibration, spontaneous rebound nystagmus, bidirectional and multiple semi-spontaneous nystagmus, abolition of optokinetic nystagmus, pendular tracking type IV, vestibular hyperfunction, absence of inhibitory effect of eye fixation, and Aubry signs in the Barany test. In the damaged neuronal structures, it is known that there is vestibular hypofunction, but little is known about when and why it occurs. A study by Fahey et al.[26] evaluated 20 patients with Friedreich's ataxia and observed that, despite the normal saccadic speed present, latency was essentially extended. In addition, vestibular alterations were found with a marked reduction in the vestibulo-ocular reflex.

A pathology study[27] of the vestibular complex and its association with its fiber bundles in four patients with SCAs, revealed that the five-core complex (interstitial, lateral, medial, spinal and superior vestibular nuclei) had suffered neurodegeneration resulting from the disease. This indicated that all bundles of fibers associated with the ascending tract of Deiters inputs, juxtarestiform body, lateral and medial vestibulospinal tracts, medial longitudinal fasciculus, and the vestibular portion of cranial nerve VIII all suffered widespread neuronal loss and atrophy that caused demyelination of the structures. These lesions may explain the brainstem changes, postural instability with imbalance, oculomotor deficits and the presence of the pathological vestibulo-ocular reflex.

Zeigelboim et al.[16] stated that the loss of hair cells of the ampullary crests and maculae, a decline in the number of nerve cells in the vestibular (or Scarpa's) ganglion, the degeneration of the otoliths, reduced labyrinthine blood flow, progressive depression of neural stability, and the reduction in compensation capacity in the vestibulo-ocular reflex and vestibulospinal reflexes all contribute to the reduction of the speed of the eye tracking motion and rotational and caloric hyporeactivity of the both peripheral and central vestibular systems – characteristics presenting in both hereditary ataxias. Luis et al.[28] pointed to the vestibulo-ocular reflex alteration as a neurophysiological biomarker for disease severity.

Other studies[16,24] reported that lesions in the cerebellar vermis caused ataxia of the upper limbs, head tremors, dysmetria, and trembling eye movements. It was this part of the anatomy that showed electrical activity along the length of the eye muscles and neck.

In the present study, when comparing the results of the vestibular examination in both hereditary ataxias, we observed a significant difference in central vestibular dysfunction. These findings agree with other studies[25] that showed involvement of the central vestibular system, and stress the importance of vestibular evaluations in diseases affecting the posterior fossa. Some authors[26] stressed that the range of changes in eye movements suggested changes in the

brain stem, as well as the cortical and vestibular pathways. It is known that the central vestibular pathway comprises the vestibular nuclei in the vestibular area of the brainstem rhomboid fossa, vestibulo-oculomotor, vestibulocerebellar, vestibuloreticular, vestibulocortical, vestibulospinal pathways and their connections with the reticular formation (reflex mechanisms, including autonomous ones) and other areas of the CNS. The CNS quickly organizes and processes visual, vestibular and proprioceptive sensory information in specific areas of the brainstem and cerebellum, which orient head, neck, cervical spine, legs, arms, eyes and all body muscle movements[29]. Regarding gender, there was no literature with which to compare our results.

In conclusion, the most evident neurological symptoms found in this group of patients with hereditary ataxias were gait disturbances, dizziness, dysarthria and dysphagia.

Alterations in vestibular examinations occurred in 87% of patients, mostly in the caloric test (79%), with a predominant deficit of central vestibular system dysfunction (70%).

This underscores the importance of the contribution of topodiagnostic labyrinthine evaluations for neurodegenerative diseases as, in most cases, the initial symptoms are otoneurological.

References

1. Teive HA, Ashizawa T. Primary and secondary ataxias. Curr Opin Neurol. 2015 Aug;28(4):413-22. https://doi.org/10.1097/WCO.0000000000000227
2. Haerer AF. The neurologic examination. 5th ed. Philadelphia: J.B. Lippincott;1992.
3. Zeigelboim BS, Teive HA, Santos R, Arruda WO, Jurkiewicz AL, Mengelberg H et al. Avaliação audiológica na ataxia espinocerebelar. CoDAS. 2013;25(4):351-7. https://doi.org/10.1590/S2317-17822013005000001
4. Zeigelboim BS, Souza SD, Mengelberg H, Teive HA, Liberalesso PB. Vestibular rehabilitation with virtual reality in spinocerebellar ataxia. Audiol Commun Res. 2013 Apr.-June;18(2):143-7. https://doi.org/10.1590/S2317-64312013000200013
5. Teive HA, Munhoz RP, Arruda WO, Lopes-Cendes I, Raskin S, Werneck LC et al. Spinocerebellar ataxias: genotype-phenotype correlations in 104 Brazilian families. Clinics (Sao Paulo). 2012;67(5):443-9. https://doi.org/10.6061/clinics/2012(05)07
6. Embiruçu EK, Martyn ML, Schlesinger D, Kok F. Autosomal recessive ataxias: 20 types, and counting. Arq Neuropsiquiatr. 2009 Dec;67(4):1143-56. https://doi.org/10.1590/S0004-282X2009000600036
7. Ell J, Prasher D, Rudge P. Neuro-otological abnormalities in Friedreich's ataxia. J Neurol Neurosurg Psychiatry. 1984 Jan;47(1):26-32. https://doi.org/10.1136/jnnp.47.1.26
8. Rinaldi C, Tucci T, Maione S, Giunta A, De Michele G, Filla A. Low-dose idebenone treatment in Friedreich's ataxia with and without cardiac hypertrophy. J Neurol. 2009 Sep;256(9):1434-7. https://doi.org/10.1007/s00415-009-5130-6
9. Albano LM, Zatz M, Kim CA, Bertola D, Sugayama SM, Marques-Dias MJ et al. Friedreich's ataxia: clinical and molecular study of 25 Brazilian cases. Rev Hosp Clin Fac Med Sao Paulo. 2001 Sep-Oct;56(5):143-8. https://doi.org/10.1590/S0041-87812001000500003
10. Fortuna F, Barboni P, Liguori R, Valentino ML, Savini G, Gellera C et al. Visual system involvement in patients with Friedreich's ataxia. Brain. 2009 Jan;132(Pt 1):116-23. https://doi.org/10.1093/brain/awn269
11. Pandolfo M. Friedreich ataxia. Arch Neurol. 2008 Oct;65(10):1296-303. https://doi.org/10.1001/archneur.65.10.1296
12. Arruda WO. CarvalhoNeto A. Late on set autosomal dominant cerebellar ataxia. Neurobiol. 1991 jan-mar;54(1):35-44.
13. Freud AA. Diagnóstico molecular das ataxias espinocerebelares tipos 1, 2, 3, 6 e 7: estudo populacional e em indivíduos com suspeita clínica [tese]. Curitiba: Universidade Federal do Paraná; 2007.
14. Harada H, Tamaoka A, Watanabe M, Ishikawa K, Shoji S. Downbeat nystagmus in two siblings with spinocerebellar ataxia type 6 (SCA 6). J Neurol Sci. 1998 Oct;160(2):161-3. https://doi.org/10.1016/S0022-510X(98)00250-0
15. Schelhaas HJ, Ippel PF, Beemer FA, Hageman G. Similarities and differences in the phenotype, genotype and pathogenesis of different spinocerebellar ataxias. Eur J Neurol. 2000 May;7(3):309-14. https://doi.org/10.1046/j.1468-1331.2000.00067.x
16. Zeigelboim BS, Jurkiewicz AL, Fukuda Y, Mangabeira-Albernaz PL. [Vestibular disorders in degenerative diseases of the central nervous system structures]. Pro Fono. 2001 Sep;13(2):263-70. Portuguese.
17. Dueñas AM, Goold R, Giunti P. Molecular pathogenesis of spinocerebellar ataxias. Brain. 2006 Jun;129(Pt 6):1357-70. https://doi.org/10.1093/brain/awl081
18. Schöls L, Bauer P, Schmidt T, Schulte T, Riess O. Autosomal dominant cerebellar ataxias: clinical features, genetics, and pathogenesis. Lancet Neurol. 2004 May;3(5):291-304. https://doi.org/10.1016/S1474-4422(04)00737-9
19. Pulst SM. Introduction to medical genetics and methods of DNA testing. In: Pulst SM, editor. Genetics of movement disorders. Amsterdan: Academic Press; 2003. p. 1-18.
20. Mangabeira-Albernaz PL, Ganança MM, Pontes PA. Modelo operacional do aparelho vestibular. In: Mangabeira-Albernaz PL, Ganança MM, editors. Vertigem. 2nd ed. São Paulo: Moderna; 1976. p. 29-36.
21. Ganança CC, Souza JA, Segatin LA, Caovilla HH, Ganança MM. Normal limits of parameters for evaluation with digital electronystagmography neurograff. Acta AWHO. 2000;19:105.
22. Nakamagoe K, Iwamoto Y, Yoshida K. Evidence for brainstem structures participating in oculomotor integration. Science. 2000 May;288(5467):857-9. https://doi.org/10.1126/science.288.5467.857
23. Houssay BA. Fisiologia humana. 7a ed. Buenos Aires: El Ateneo; 1984.
24. Oppenheimer DR. Greenfield's neuropathology. 3rd ed. Chicago: Edward Arnold; 1976.
25. Zeigelboim BS, Teive HA, Carvalho HA, Abdulmassih EM, Marques JM, Cardoso RC. Vestibular findings in autosomal recessive ataxia. Int Tinnitus J. 2013;18(2):156-62. https://doi.org/10.5935/0946-5448.20130020
26. Fahey MC, Cremer PD, Aw ST, Millist L, Todd MJ, White OB et al. Vestibular, saccadic and fixation abnormalities in genetically confirmed Friedreich ataxia. Brain. 2008 Apr;131(4):1035-45. https://doi.org/10.1093/brain/awm323 PMID:18238798
27. Buttner N, Geschwind D, Jen JC, Perlman S, Pulst SM, Baloh RW. Oculomotor phenotypes in autosomal dominant ataxias. Arch Neurol. 1998 Oct;55(10):1353-7. https://doi.org/10.1001/archneur.55.10.1353
28. Luis L, Costa J, Muñoz E, de Carvalho M, Carmona S, Schneider E et al. Vestibulo-ocular reflex dynamics with head-impulses discriminates spinocerebellar ataxias types 1, 2 and 3 and Friedreich ataxia. J Vestib Res. 2016 Jul;26(3):327-34. https://doi.org/10.3233/VES-160579
29. Jurkiewicz AL, Floriani A, Collaço LM, Zeigelboim BS. Anatomia funcional da orelha. In: Zeigelboim BS, Jurkiewicz AL (org). Multidisciplinaridade na otoneurologia. São Paulo: Roca; 2012. p. 19-95.