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Vestibular findings in autosomal recessive ataxia

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Abstract

Objective: This study aims to examine vestibular disorders in patients with recessive spinocerebellar ataxia. **Design:** A retrospective cross-sectional study was conducted. The patients underwent the following procedures: case history, ENT and vestibular evaluations. **Study sample:** The tests were performed in 19 patients ranging from 6 to 63 years of age (mean age of 36.7). **Results:** Clinically, the patients commonly had symptoms of dizziness (57.8%), lack of coordination of movement with imbalance when walking (52.6%), and headaches (42.1%). In vestibular testing, alterations were predominantly evident under caloric testing (73.5%), rotational chair testing, and testing for gaze and optokinetic nystagmus (36.8%). The presence of alterations occurred under examination in 89.5% of these patients, 100% occurred in subjects with Friedreich's ataxia and 84.6% for subjects with indeterminate recessive spinocerebellar ataxia, with the majority occurring in those with central vestibular dysfunction, 57.9% of the examinations. **Conclusion:** The most evident neurotological symptoms were dizziness, lack of coordination of movement, and imbalance when walking. Alterations in vestibular examinations occurred in 89.5% of patients, mostly in the caloric test, with a predominance of deficient central vestibular system dysfunction. This underscores the importance of the contribution of topodiagnostic labyrinthine evaluations for neurodegenerative diseases.

Keywords: ataxia, spinocerebellar ataxias, spinocerebellar degenerations, vertigo, vestibular function tests.

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INTRODUCTION

Hereditary ataxias correspond to roughly 10% of genetic diseases that affect the nervous system. Currently there are over 20 different types of autosomal recessive ataxias that have been mapped and classified according to their pathogenesis[1]. In this group of diseases, some are very rare, being observed only in isolated populations, whereas others are found worldwide[2]. Among them, is Friedreich's ataxia (FA) initially described by Nicholaus Friedreich in 1863, however only becoming known around 1882. It is a neurodegenerative disease that is progressive in nature, and has autosomal recessive heredity, with early onset in most cases[2-4].

The mutation responsible for this disease is found on chromosome nine where an expansion of a GAA trinucleotide repeat in the X25 gene occurs. Subjects without this mutation have 17-22 repetitions, whereas those affected by this disease have, on average, 700-1000 GAA trinucleotide repeats[5]. The affected gene's function is to encode mitochondrial protein, frataxin, which is involved in iron metabolism[2-5]. The deficit of this protein causes the accumulation of iron in mitochondria compromising the mitochondrial respiratory chain and increasing oxidative stress[2,6,7].

The first symptoms are usually observed in childhood or the early teen years, however, in some cases, the diagnosis can be made before the age of two or after twenty. The main features of the disease are: ataxia (impaired coordination) which initially affects the lower limbs and subsequently the higher limbs, absence of tendon reflexes, and weakness in the lower limbs, dysarthria, loss of deep distal sensitivity and bilateral Babinski sign. Nerve conduction studies show axonal sensory neuropathy[5,6,8]. Other characteristics that can be attributed to cases are: nystagmus, optic atrophy, hearing loss (may be present), atrophy in the hands and distally in the lower limbs, scoliosis, *pes cavus*, and claw toes[2-8]. Diabetes may be present in 10% of cases, and cardiomyopathy occurs in approximately two thirds of patients being the leading cause of death[7-9]. There are significant variations in the average duration of disease, and the onset of symptoms until death, which that tends to occur around the fourth decade of life[5-7,10].

The diagnosis of FA is performed by means of clinical and genetic data.

The spinocerebellar ataxias (SCAs) are part of a list of diseases that, by their manifestations and areas of impairment, may cause vestibular alterations, with labyrinth exams being an important tool in confirming vestibular disorders and their relationship with the central nervous system. The tests that make up the vestibular examination permit the assessment of the relationship between balance and the function of the posterior labyrinth, vestibular branches of the eighth cranial nerve, vestibular nuclei of the floor of the fourth ventricle, the vestibular pathways, and, especially, vestibuloocular, vestibulocerebellar, vestibulospinal, and vestibuloproprioceptive-cervical interrelationships[11]. Lesions to the cerebellum cause ataxia of the upper limbs, head titubation, dysmetria, and tremors in eye movements, which is the part of the anatomy that shows electrical activity along the ocular muscles and neck. Some evidence suggests that lesions in the cerebellar vermis cause vertical dysmetria while more lateral or paravermian lesions cause horizontal dysmetria. Moreover, the more anterior the lesion, the more intense the dysmetria will appear in the upper eye, whereas the more posterior the lesion, the more intense the dysmetria will appear in the lower eye[12].

See vestibular disorders in patients with recessive spinocerebellar ataxia.

PATIENTS AND METHOD

A retrospective cross-sectional study was conducted. We evaluated 19 patients (7 females and 12 males) who were referred from the Neurology Service, Department of Clinical Medical from the Clinical Hospital for review at the Otoneurology Research Center, a teaching institution in the same city, with a diagnosis of recessive SCA. Of these patients, six were diagnosed with Friedreich's ataxia (FA). The diagnosis of ataxia was performed by means of genetic testing using the Polymerase Chain Reaction (PCR) technique[13-15]. Thirteen patients are currently undergoing genetic research to know what type of recessive SCA they have and, therefore, belong to the undetermined SCA group. The ages of the patients ranged from six to 63 years old, with a mean age of 36.7.

A questionnaire to obtain otoneurological symptoms and personal and family information was applied. Otorhinolaryngological evaluation was performed to exclude any alteration that could interfere with the exams.

Patients undertook a special diet, starting 72 hours before the otoneurological exams (abstaining from the intake of coffee, any kind of soda or caffeinated tea, chocolate, smoke, or alcohol). Analgesics, tranquilizers, and antihistaminic and antivertigo medications were suppressed during this period to minimize possible interferences with the test results. Three hours of fasting was recommended prior to the exam.

Vestibular function evaluation is composed of many labyrinthine function and ocular tests. The first part of our patients' evaluation was simply clinical and consisted of a systematic search for spontaneous, gaze,

and positional nystagmus. The second part consisted of interpretation of the ENG test results, which is the objective register of the variations in the corneoretinal potentials, captured by sensitive electrodes. The ENG test is composed of: calibration of the ocular movements, search for spontaneous and gaze nystagmus, the oscillatory tracking test, optokinetic nystagmus search, and rotatory and caloric tests.

We obtained formal written informed consent from all participating subjects, and the research project was approved by the Ethics Committee on Research Involving Human Subjects (registration number CEP 058/2008).

Clinical Evaluation

The search for positional nystagmus and vertigo was verified through Brandt and Daroff's maneuver[16]. Patients were requested to remain seated with the head and neck bent and the body tilted to the side, which evokes the vertigo; the head was then positioned 45 degrees in the opposite direction, and the neck rested on a horizontal plane at the final position. Patients returned to the first position and repeated the procedure toward the opposite side. The clinician searched for nystagmus for 30 seconds in each position.

The search for spontaneous nystagmus occurred without specific stimulation, with open and closed eyes. We searched for horizontal and vertical gaze nystagmus with 30-degree deviations (right, left, up, and down).

ENG Registers

We performed ENG with three-channel equipment (Berger Eletromedicina, model VN316, made in São Paulo, São Paulo, Brazil). We cleaned the periorbital region with alcohol and placed the electrodes with electrolytic paste at the lateral angle of each eye and in the midpoint of the frontal line, forming a triangle and enabling the register of horizontal, vertical, and oblique ocular movements.

We performed tests with a rotatingchair (Ferrante, model COD 14200, made in São Paulo, SP, Brazil), a visual stimulator (Neurograff Eletromedicina, model EV VEC, São Paulo, SP, Brazil), and air caloric stimulator (Neurograff Eletromedicina, model NGR 05, São Paulo, SP, Brazil).

Calibration of the ocular and saccadic movements is based on the capture of the variations of electric potential between the cornea and the retina. We requested patients to keep the head still while visually tracking a light target moving in horizontal direction and then in vertical direction. The equipment is adjusted so that the eyes' movement performs an angle of 10 degrees (standard calibration). As these movements are registered, we adjust the gain of the graphic needle to 10-mm amplitude (first channel) and to 5-mm amplitude (second and third channels). A variation of 1 degree corresponds to a displacement of 1 mm in the graphic, registered on paper, set under a speed of 5 mm/sec. To ensure the constancy of the distance between both targets and between the patient and the targets, we used the following formula: $x = 2y.tg5$, where x is the distance between the targets and *y* is the distance between the patient and the target and tg is tangent. To evaluate the regularity of the saccadic movements, we used the normal ranges of the following parameters: latency, accuracy, and velocity of movement.

The normal velocity range for spontaneous nystagmus search is less than 7 degrees per second with closed eyes. Gaze nystagmus is expected to be absent with open eyes. Occurrence, direction, inhibiting effect of ocular fixation (IEOF), and maximum slow component angular velocity of nystagmus (MSCAV) were registered.

For the oscillatory tracking test, we requested patients to visually track oscillatory targets in the visual stimulator, and we registered the ocular movements. The type and gain of the ocular movements were observed in the following frequencies: 0.20, 0.40, and 0.80 Hz. The test is used to evaluate the integrity of the oculomotor system in controlling the slow movements of the eyes. The normal standards are nystagmus types I and II.

In the optokinetic nystagmus search, we requested that patients track multiple targets (three horizontal streams of lighted dots) moving forward and backward. The symmetry and gain of the nystagmus were observed. Occurrence, directional preponderance, and measurements of the MSCAV of nystagmus were evaluated. To calculate the directional preponderance, we used the Jongkees formula[17] detailed below.

[EQ] $DP = [(MSCAVccw-MSCAVcw)/(MSCAVccw + MSCAVcw)] * 100\%$

where DP: Directional preponderance; MSCAVccw: Maximum slow-component angular velocity, counterclockwise; MSCAVcw: Maximum slow-component angular velocity, clockwise [/EQ]; Values of less than 20 degrees per second are considered normal for this test.

In the rotation test, patients' heads were laterally tilted 30 degrees to stimulate lateral semicircular ducts (right anterior and left posterior), in which the variations of angular acceleration are sensed. After that, patients' heads were positioned 60 degrees backward and 45 degrees to the right and left sides so that the vertical semicircular canals were stimulated. The oscillatory stimulation started at 180 degrees and progressively decreased to 0. We observed the presence, directional preponderance, and frequency of the ocular movements, using the same formula for optokinetic nystagmus search. The normal range for this test is under 33%.

The caloric test requires patients to be positioned with head and body tilted 60 degrees

backward (Brunning's position I) for proper stimulation of the lateral semicircular canals[18]. The air stimuli were set at the temperatures of 42 °C, 18 °C, and 10 °C, lasting 80 seconds. Records were registered with open and closed eyes to note IEOF, direction, MSCAV absolute values, and correlation between directional preponderance and post caloric nystagmus direction. Normal absolute values are within 2 degrees and 24 degrees per second, whereas normal relative values are lower than 41% for labyrinth preponderance and less than 36% for nystagmus directional preponderance.

We compared results with normal standards, obtained from epidemiological studies for the Brazilian population[19-21]. Table 1 shows the criteria used to analyze each test as well as to distinguish central from peripheral vestibulopathy.

The diagnosis of peripheral vestibulopathy is achieved by comparison with normal standards and the absence of pathognomonic signs of central vestibular alterations.

Statistical Analysis

We applied the Difference of Proportions Test for the purpose of comparing the vestibular examination results (analyzing normal and abnormal results) and correlating the type of recessive ataxia with the most abnormal results in the vestibular examination (caloric, rotational, optokinetic, and gaze nystagmus) and then, with symptoms of dizziness, lack of coordination of movement with imbalance when walking. 0.05, or 5%, was the rejection level for the null hypothesis.

RESULTS

The most mentioned complaints in the case history were dizziness (57.8%), lack of coordination of movement with imbalance when walking (52.6%), and headache (42.1%), as shown in Table 2.

For vestibular function, in testing for spontaneous, gaze, optokinetic, rotational, caloric, and oscillatory tracking nystagmus, results were altered in both SCA groups, as shown in Table 3.

Table 1. Normal standards and criteria used to analyze the vestibular tests and distinguish central from peripheral.

	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 (< 7 degrees/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 retractor)
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 superposed 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

Based on Padovan & Pansini[19], Mangabeira-Albernaz et al.[20], and Ganança et al.[21].

Table 2. Distribution of the frequency of symptoms in 19 patients with recessive spinocerebellar ataxia (SCA).

Symptoms	Number of Patients	Frequency (%)
Dizziness	11	57.8
Lack of coordination of movement	10	52.6
Imbalance when walking	10	52.6
Headache	8	42.1
Dysarthria	7	36.8
Dysphagia	7	36.8
Tremors	6	31.5
Falling	6	31.5
Doublé vision	5	26.3
Pain radiating to the shoulder and arm	5	26.3
Fatigue	5	26.3
Depression	4	21.0
Anxiety	4	21.0
Difficulty moving neck	4	21.0
Hearing loss	3	15.7
Cracking in neck	3	15.7
Tingling in extremities	3	15.7
Insomnia	1	5.2
Olfactory alteration	1	5.2
Taste alteration	1	5.2

Table 3. Distribution of the frequency of changes in vestibular examinations in 19 patients with recessive spinocerebellar ataxia (SCA).

Altered Results	FA		UND		SCAT	
	n	%	n	%	n	%
Multiple gaze nystagmus	4	67.0	3	23.0	7	36.8
Bilateral labyrinthine hyporeflexia	3	50.0	6	46.1	9	47.3
Rotational nystagmus absent	3	50.0	4	30.7	7	36.8
Optokinetic asymmetrical nystagmus	3	50.0	4	30.7	7	36.8
Pendular tracking altered	2	33.4	1	7.6	3	15.7
Spontaneous nystagmus present	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

FA: Friedreich's Ataxia; UND: Undefined ataxia; SCAT: Spinocerebellar ataxia total; n: Number; % frequency. In the application of the Difference of Proportions Test, it was shown that there was no difference in the correlation between the type of recessive ataxia with ocular and labyrinthine evidence that showed a higher frequency of alterations than the others, caloric ($p = 0.8730$), rotational ($p = 0.42865$), optokinetic ($p = 0.4286$), and gaze nystagmus ($p = 0.1828$).

For the abnormal results in both SCAs, the highest prevalence occurred in the caloric test (73.5%) with a predominance of labyrinthine hypofunction (47.3%), and in the rotation test (36.8%), which shows a lack of response for the lateral, anterior, and posterior semicircular canals, and later, in the testing for gaze and optokinetic nystagmus (36.8%), demonstrating an alteration in tracking movements, as shown in Table 3.

In the application of the Difference of Proportions Test, it can be seen that there was no difference in the correlation between the type of recessive ataxia with ocular and labyrinthine results that showed one having a higher frequency of alterations than another, caloric ($p = 0.8730$), rotational ($p = 0.42865$), optokinetic ($p = 0.4286$), and gaze nystagmus ($p = 0.1828$).

Regarding the result of vestibular examination, we observed a higher incidence of central vestibular dysfunction (57.9%), as shown in Table 4.

Table 4. Frequency of results in vestibular examinations in 19 patients with recessive spinocerebellar ataxia (SCA).

Vestibular Exam Result	FA		UND		SCAT	
	n	%	n	%	n	%
Central vestibular dysfunction	4	66.6	7	53.8	11	57.9
Peripheral vestibular dysfunction	2	33.4	4	30.8	6	31.6
Normal vestibular exam	-	-	2	15.4	2	10.5

FA: Friedreich's Ataxia; UND: Undefined ataxia; SCAT: Spinocerebellar ataxia total; n: Number; % frequency. In the application of the Difference of Proportions Test, it was shown that there was a significant difference in the proportions of normal and altered exams ($p = 0.0000$).

The application of the Difference of Proportions Test proves that there was a significant difference between the proportions of normal and abnormal tests ($p = 0.0000$).

The correlation between Friedereich and undetermined ataxias with the three most evident neurotological symptoms can be seen in Table 5.

Table 5. Correlation between most evident neurotological symptoms in 19 patients with recessive spinocerebellar ataxia (SCA).

Type of Lack of Coordination in Movement	Dizziness		Lack of Coordination in Movement		Imbalance in Walking	
	n	%	n	%	n	%
Friedreich's Ataxia	2	33.4	2	33.4	3	50.0
Undefined Ataxia	9	69.2	8	61.5	7	53.8

n: Number of patients; %: frequency. In the application of the Difference of Proportions Test, proves that there was no difference in the correlation between recessive ataxias with symptoms of dizziness ($p = 0.1582$), lack of coordination of movement ($p = 0.2554$), and imbalance when walking ($p = 0.8730$).

In the application of the Difference of Proportions Test, it is shown that there was no difference in the correlation between the recessive ataxias with symptoms of dizziness ($p = 0.1582$), lack of coordination of movement ($p = 0.2554$), and imbalance when walking ($p = 0.8730$).

The correlation between the results of the ENG test in the three most evident neurotological symptoms showed that 89.5% of abnormal tests, 52.6% had dizziness and incoordination of movements and 47.3% gait imbalance.

DISCUSSION

The most reported symptoms by patients were also observed in several studies[22-25]. Because of its multidisciplinary clinical form, various events may occur with disease progression.

The combination of vestibular dysfunction with the presence of cerebellar atrophy may contribute significantly to the onset of gait instability, which is one of the initial symptoms of SCAs[26].

In the present study, the ENG test observed a higher prevalence of vestibular dysfunction (47.3%), as well as abnormal gaze, optokinetic, and rotational nystagmus (36.8%). Lesions of the cerebellar vermis cause ataxia of the upper limbs, head titubation, dysmetria, and tremors in eye movements, and it is this anatomical part that expresses the extent electrical activity of the eye and neck muscles (Cogan et al., 1982). The most evident changes in other studies[11,12,25] were the presence of positional nystagmus, irregular eye movement calibration, spontaneous rebound nystagmus, bidirectional and multiple gaze nystagmus, and the abolition of optokinetic nystagmus, pendular tracking type IV, vestibular hypofunction, the absence of the inhibitory effect for ocular fixation, and signs of Aubry for proof of Barany. Among the damaged neuronal structures, the occurrence of vestibular hypofunction is known, but little is known about when and why it occurs. Takegoshi & Murofushi[27] note that spinocerebellar degeneration is one of the clinical entities for disorders of the vestibular system.

Prim-Espada et al.[28] performed an electrooculography exam (EOG) on 51 patients genetically diagnosed with FA and observed saccadic movements, for those with positional, optokinetic, and spontaneous nystagmus. The authors reported suppression of the vestibulo-ocular reflex (VOR) in all subjects. Fahey et al.[29] evaluated 20 patients with FA and observed that despite the presence of normal saccadic velocity, latency was shown to be essentially extended. In addition, vestibular abnormalities were observed with a sharp reduction in the gain of the VOR. Abnormal saccadic latency may be useful as a marker of severity and progression in FA[30].

Zeigelboim et al.[11] reported that the loss of hair cells in the cristae ampullaris and maculae, the decline in the number of nerve cells in the vestibular ganglion (Scarpa), the degeneration of the otoliths, reduced labyrinthine blood flow, progressive depression of neural stability, and the reduction in the ability to compensate for vestibulo-ocular and vestibule-spinal reflexes all contribute to reducing the speed of tracking movements and for rotational and caloric hyporeactivity of both the peripheral and central vestibular systems, which is present in SCAs.

In the present study, when comparing the result of vestibular evaluations with recessive SCAs, this differ ence became significant for central vestibular dysfunction. Ito et al.[25] showed involvement of the central vestibular system and stressed the importance of vestibular evaluation in diseases that involve the posterior fossa. Prim-Espada et al.[28] observed central alterations in EOG examinations in 72.5% of patients, while Monday & Lemieux[31] by means of ENG testing saw alterations in 100% of their cases. Fahey et al.[29] emphasized that the range of alterations in eye movements suggest changes in the brainstem, as well as cortical and vestibular pathways.

In the present study, no significance was observed in correlation with the most obvious neurotological symptoms (dizziness, lack of coordination of movement and imbalance when walking) with recessive SCAs. No references were found that could compare to our findings.

It was evident that changes in the ENG are related to the severity of SCAs or the clinical stage of the disease. We emphasize the importance of studying the concomitant vestibular system in clinical and genetic tracking.

CONCLUSION

The most evident neurotological symptoms were dizziness, lack of coordination of movement and imbalance when walking.

Alterations in vestibular examinations occurred in 89.5% of patients, being found in the caloric test, with a predominance of central vestibular system dysfunction deficiency.

This underscores the importance of the contribution of the labyrinthine evaluation for topodiagnosis of neurodegenerative diseases since in most cases the initial symptoms are neurotological, and also in the choice of procedures to be performed in clinical and therapeutic monitoring.

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Conflict of interest

The authors report no declarations of interest.

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