

# Otoneurological Abnormalities in Patients with Friedreich's Ataxia

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## Abstract

**Introduction** Friedreich's ataxia is a neurodegenerative disease and progressive by nature. It has autosomal recessive inheritance and early onset in most cases. Nystagmus and hearing loss (in some cases) make up some of the common symptoms seen in this disorder.

**Objective** The objective of this study is to examine vestibular disorders in patients with Friedreich ataxia.

**Methods** We conducted a retrospective cross-sectional study. We evaluated 30 patients with ages ranging from six to 72 years (mean age of 38.6 (± 14.7)). The patients underwent the following procedures: anamnesis, ENT, and vestibular evaluations.

**Results** Clinically, the patients commonly had symptoms of incoordination of movement (66.7%), gait disturbances (56.7%), and dizziness (50%). In vestibular testing, alterations were predominantly evident under caloric testing (73.4%), gaze nystagmus testing (50.1%), rotational chair testing (36.7%), and optokinetic nystagmus testing (33.4%). The presence of alterations occurred under examination in 90% of subjects, with the majority occurring in those with central vestibular dysfunction (70% of the examinations).

**Conclusion** The most evident neurotological symptoms were incoordination of movement, gait disturbances, and dizziness. Alterations in vestibular examinations occurred in 90% of patients, mostly in the caloric test, with a predominance of deficient central vestibular system dysfunction.

## Keywords

- ▶ spinocerebellar ataxias
- ▶ ataxia
- ▶ spinocerebellar degenerations

## Introduction

Hereditary ataxias account for ~10% of genetic diseases that affect the nervous system. Currently, more than 20 different types of autosomal recessive ataxias are mapped and classified according to their etiology.<sup>1</sup> In this group of diseases, some are very rare and observed only in isolated populations, while others are found worldwide.<sup>2</sup> Among them, is Friedreich's ataxia (FA), described initially by Nicholas Friedreich in 1863, but only

becoming well-known around 1882. It is a neurodegenerative disease, progressive in nature, autosomal recessive, and early onset in most cases.<sup>2–4</sup>

The first symptoms are usually observed in childhood or the early teens; however, in some cases, the diagnosis is made before the age of two years or after the age of twenty. The main features of the disease are: ataxia (impaired coordination) that initially affects the lower limbs and then the upper limbs, absence of tendon reflexes and weakness in the lower

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limbs, dysarthria, loss of distal deep sensitivity, and bilateral Babinski sign. Nerve conduction studies show axonal sensory neuropathy.<sup>5-7</sup> Other main problems associated to the condition are: nystagmus, optic atrophy, hearing loss (which may be present), atrophy in hands and distal lower limbs, scoliosis, pes cavus, and claw toes.<sup>2-7</sup> Diabetes is present in 10% of cases and cardiomyopathy occurs in approximately two-thirds of patients, making the latter the leading cause of death.<sup>7-9</sup> There are significant variations in the average duration of the disease, from the onset of symptoms until death, which tends to occur around the fourth decade of life.<sup>5,6,8,10</sup>

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

Spinocerebellar ataxias (SCAs) are part of a list of diseases that, by their manifestations and impairment areas, can lead to vestibular disorders. The vestibular evaluation is an important tool in confirmation of vestibular disorders and their relationship with the central nervous system. The tests that comprise the vestibular examination make it possible to assess balance and its relationship to the function of the posterior labyrinth, vestibular branches of cranial nerve VIII, vestibular nuclei at the floor of the fourth ventricle, vestibular pathways and, above all, vestibular-oculomotor, vestibulocerebellar, vestibulospinal, and vestibular and neck proprioceptive relationships.<sup>11</sup>

The aim of this study was to investigate the vestibular disorders in patients with Friedreich's ataxia.

## Materials and Methods

This study was approved by the Institutional Ethics Committee under registration number 058/2008 and authorized by the patients' signing of a consent form.

A retrospective cross-sectional study was conducted. We evaluated 30 patients (10 female and 20 male) directed by the Department of Internal Medicine at the Hospital de Clinicas for evaluation by the Otoneurology Department of an educational institution in the same city, with a diagnosis of Friedreich's-type recessive SCA (FA). The diagnosis of ataxia was performed by means of genetic testing using Polymerase Chain Reaction (PCR) (► **Table 1**).<sup>12-14</sup> To measure the severity of cerebellar ataxia in an easier and more practical manner, Schmitz-Hübisch et al.<sup>15</sup> proposed a scale for the assessment and rating of ataxia (SARA) which was translated and validated in Brazilian Portuguese by Braga-Neto et al.<sup>16</sup> The SARA has eight questions that yield a total score of 0 (no ataxia) to 40 (most severe ataxia); 1: gait (score 0 to 8), 2: stance (score 0 to 6), 3: sitting (score 0 to 4), 4: speech disturbance (score 0 to 6), 5: finger-chase test (score 0 to 4), 6: nose-finger test (score 0 to 4), 7: fast alternating hand movements (score 0 to 4), 8: heel-shin coordination test (score 0 to 4). Kinetic limb functions (items 5 to 8) are rated independently for both sides, and the arithmetic mean of both sides is included in the SARA total score.<sup>15</sup> This scale has proven to be a valid and trustworthy measurement in SCA patients.

Excluded from the study were patients that presented with otological alterations or other abnormalities that prevented the completion of testing.

The following procedures were performed:

**Table 1** Aspects of Friedreich's ataxia

CASE	AGE (years)	SEX	DISEASE DURATION (years)	SARA
1	43	M	25	20
2	41	M	7	3,5
3	30	F	18	8
4	24	M	8	4
5	29	M	13	14
6	17	M	3	13
7	63	F	38	7
8	6	F	6	19
9	37	F	19	16
10	41	F	20	29,5
11	27	F	12	14
12	25	F	12	12
13	55	F	30	7
14	44	M	10	3,5
15	55	M	12	14
16	37	M	17	19
17	51	M	30	29
18	27	M	10	16
19	46	M	18	10
20	72	M	42	28
21	52	F	18	3
22	30	M	4	4,5
23	37	M	19	18
24	44	M	18	9,5
25	22	M	14	5
26	42	F	31	25
27	63	M	18	19
28	42	M	21	8
29	28	M	21	8
30	30	M	17	13

Abbreviations: F, female; M, male; SARA, scale for the assessment and rating of ataxia.

### Anamnesis

A questionnaire was given focusing on otoneurological signs and symptoms (► **Fig. 1**).

### Ear, Nose, and Throat (ENT) Evaluation

An ENT evaluation was performed to rule out any alterations that could affect the test.

### Vestibular Assessment

Patients underwent the following tests that make up the vestibular examination. Initially, we checked vertigo and spontaneous and semi-spontaneous positional nystagmus.

Then, to analyze vectoelectronystagmography (VENG), we used a three-channel thermosensitive Berger VN316 model

ANAMNESIS			
<b>I. Identification</b>		Date: / /	
Name: _____			
Age: _____		Date of Birth: _____	
Country of Birth: _____		Race: _____	
Occupation: _____			
<b>II. Professional Activity</b>			
Previous jobs: _____			
Total time working: in noisy place _____		exposed to chemical agents: _____	
Is currently ( ) or has been ( ) exposed to chemical agents: _____			
heavy metals (lead, mercury): _____		asphyxiant (e.g. CO <sub>2</sub> ): _____	
<b>III. History of Morbidity</b>			
Smokes ( ) or has been a smoker ( )?			
How many packs per day? _____		How many cigarettes per day? _____	
Consumes alcohol regularly? ( ) No ( ) Yes How much per day: _____			
Consumes caffeine? ( ) No ( ) Yes How much per day: _____			
Dietary errors: _____			
Takes medication? ( ) No ( ) Yes Which ones: _____			
Had surgery? ( ) No ( ) Yes What: _____			
Identify subject's health problems:			
Signs and Symptoms	Yes	No	Medication taken
Change in blood flow			
Hypertension			
Sensitivity change			
Incoordination of movement			
Sensation of movement of objects			
Diabetes			
Thyroid dysfunction			
Cranioencephalic trauma			
Heart disease			
Kidney damage			
Rheumatologic disorders			
Degenerative Diseases			
TMJ disorder			
Dysarthria			
Alteration in smell/ taste			
Pain / Difficulty in moving neck			
Tingling in extremities			
Dysphonia			
Dysphagia			
Double / blurred vision			
Fatigue			
Anxiety / fear / depression			
Headache / migraine			
<b>IV. Hearing Loss</b>			
Onset: _____		Locale: ( ) right ear ( ) left ear ( ) both	
Intensity: _____		Occurrence: _____ Pain in ear: ( ) Yes ( ) No	
Purging in ear: ( ) Yes ( ) No			
Appears or worsens: _____			
Triggering factors: _____			
Aggravating factors: _____			
Factors for improvement: _____			
Concomitant symptoms: _____			

Fig. 1 Anamnesis by Otoneurology Department.

**V. Dizziness**

Onset: \_\_\_\_\_ Definition: \_\_\_\_\_ Intensity: \_\_\_\_\_  
 Occurrence: \_\_\_\_\_  
 Duration: ( ) seconds ( ) minutes ( ) hours ( ) days  
 Appears or worsens: \_\_\_\_\_  
 ( ) nausea ( ) vomiting ( ) sweating ( ) gait imbalance ( ) falling  
 Triggering factors: \_\_\_\_\_  
 Aggravating factors: \_\_\_\_\_  
 Factors for improvement: \_\_\_\_\_  
 Concomitant symptoms: \_\_\_\_\_

**VI. Tinnitus**

Onset: \_\_\_\_\_ Locale: ( ) right ear ( ) left ear ( ) both ( ) close to ear ( ) head  
 Type: \_\_\_\_\_ Duration: \_\_\_\_\_  
 Definition: \_\_\_\_\_ Intensity: \_\_\_\_\_  
 Occurrence: \_\_\_\_\_  
 Appears or worsens: \_\_\_\_\_  
 Triggering factors: \_\_\_\_\_  
 Aggravating factors: \_\_\_\_\_  
 Factors for improvement: \_\_\_\_\_  
 Concomitant symptoms: \_\_\_\_\_

**VII. Non-Occupational Exposure**

Is exposed for more than four hours: ( ) motorcycle ( ) loud music ( ) tools  
 ( ) farming equipment ( ) shooting of firearms  
 What does subject do in free time? \_\_\_\_\_  
 Does the subject have hobbies? \_\_\_\_\_

**Fig. 1** (Continued)

device along with a Ferrante swivel chair, a Neurograff Eletromedicina Ltda. model EV VEC visual stimulator, and a Neurograff ear calorimeter model NGR 05 (Vn 316 model, São Paulo, Brazil) for measuring air temperature.

Next, we conducted the eye and labyrinth VENG tests, according to criteria proposed by Mangabeira-Albernaz, Ganança, and Pontes.<sup>17</sup>

\*Eye movement calibration – We verified spontaneous and semi-spontaneous nystagmus using pendular tracking, checking for pre- and post-rotatory plus pre- and post-caloric optokinetic nystagmus. We recorded the caloric stimulation time in each ear using air at 42°C and 18°C lasted 80 seconds for each temperature and responses with eyes closed and then with eyes open to observe the inhibitory effect of eye fixation (IEEF). The criteria used in the air caloric test were: absolute value between 2 and 24 degrees/ sec (<2 degrees/ sec (hyporeflexia), >24 degrees/ sec (hyperreflexia); relative values of labyrinth preponderance (LP) <41% and nystagmus directional preponderance (NDP) <36%.<sup>18</sup>

## Statistical Analysis

We used a difference of proportions test to compare the results of the vestibular examination (analyzing normal and abnormal results) and to correlate FA with the most altered results from the vestibular examination (caloric, semi-spontaneous nystagmus, rotatory, and optokinetic tests) and below, with the most frequent otoneurological symptoms (incoordination of movement, imbalance of gait, and dizziness). Finally, we applied the

Fisher test correlating the results of the vestibular examination with otoneurological symptoms of major occurrence. In all cases, we considered  $p < 0.05$  to be statistically significant.

## Results

The subjects' ages ranged from six to 72 years, with a mean age 38.6 years and a standard deviation of 14.7 years. The average duration of the disease was 17.7 years and the standard deviation was 9.4 years.

The most frequent complaints in the anamneses were incoordination of movement (66.7%), gait imbalance (56.7%), dizziness (50%), and dysarthria (46.7%), as shown in ► **Table 2**.

In assessing the vestibular function, the caloric test, spontaneous and semi-spontaneous, rotatory, optokinetic, and pendulum tracking showed alterations in FA, as shown in ► **Table 3**.

Among the tests with alterations in FA, the highest prevalence occurred in: the caloric test (73.4%) with a predominance of hyporeflexia (53.3%); then, the test for semi-spontaneous nystagmus (50.1%), with a predominance of the multiple type (40%); next, the rotatory test (36.7%), which denotes a lack of response from lateral, anterior, and posterior semicircular canals; and optokinetic (33.4%), which shows a change in pursuit movements, as observed in ► **Table 3**.

The use of the difference of proportions test proves that there was significance in the correlation between FA with labyrinthine and eye tests that showed more alterations than the others, the caloric test with rotatory ( $p = 0.0065$ ) and caloric with optokinetic ( $p = 0.0032$ ).

**Table 2** Distribution in frequency of symptoms in 30 Friedreich's ataxia patients

SYMPTOMS	NUMBER OF PATIENTS	FREQUENCY (%)
Incoordination of movement	20	66.7
Gait imbalance	17	56.7
Dizziness	15	50.0
Dysarthria	14	46.7
Headache	10	33.4
Dysphagia	9	30.0
Diplopia	9	30.0
Falling	8	26.7
Tremors	8	26.7
Depression	8	26.7
Fatigue	7	23.4
Anxiety	7	23.4
Difficulty moving the neck	6	20.0
Pain radiating to the shoulder and arm	5	16.7
Tingling in extremities	4	13.4
Insomnia	3	10.0
Neck cracking	3	10.0
Hearing loss	3	10.0
Olfactory change	2	6.7
Gustative change	2	6.7
Dysphonia	1	3.4

**Table 3** Distribution in frequency of alterations in vestibular exam in 30 patients with Friedreich's ataxia

ALTERED EXAMS	FRIEDREICH'S ATAXIA	
	N	%
Bilateral labyrinthine hyporeflexia	16	53.3
Multiple semi-spontaneous nystagmus	12	40.0
Absent rotary nystagmus	11	36.7
Asymmetrical optokinetic nystagmus	10	33.4
Spontaneous nystagmus	6	20.0
Pendulum tracking alterations	5	16.7
Bilateral labyrinthine hyperreflexia	5	16.7
Bidirectional semi-spontaneous nystagmus	2	6.7
Unidirectional semi-spontaneous nystagmus	1	3.4
Unilateral labyrinthine hyperreflexia	1	3.4

Abbreviations: %, frequency; N, number of patients.

Regarding the outcome of the vestibular examination, there was a higher incidence of central vestibular dysfunction (70%), as shown in ► **Table 4**.

The implementation of the difference of proportions test proves that there was a significant difference between the proportions of normal tests and those that showed alterations ( $p = 0.0000$ ).

The correlation between FA and the three most frequent otoneurological symptoms, can be seen in ► **Table 5**.

The implementation of the difference of proportions test proves that there was no significant difference in the correlation between FA symptoms of incoordination of movement and gait imbalance ( $p = 0.42890$ ), gait imbalance and dizziness ( $p = 0.6049$ ), and dizziness and incoordination of movement ( $p = 0.1867$ ).

The result of the vestibular examination and the most frequent otoneurological symptoms is shown in ► **Table 6**.

In the application of Fisher's test, there was no significant difference in the correlation between the results of the entrance examination with the symptoms of incoordination of movement and gait imbalance ( $p = 0.4595$ ), incoordination of movement and dizziness ( $p = 0.4286$ ), and gait imbalance and dizziness ( $p = 0.7258$ ).

**Discussion**

The most commonly reported symptoms by patients were also observed in several other studies.<sup>19-22</sup> Because of the illness' multidisciplinary clinical characteristics, various events may occur with disease progression.

**Table 4** Frequency of results from vestibular exam in 30 patients with Friedreich's ataxia

VESTIBULAR EXAM RESULT	FRIEDREICH'S ATAXIA	
	N	%
Central vestibular disorder	21	70.0
Peripheral vestibular disorder	6	20.0
Normal vestibular exam	3	10.0
Total	30	100.0

Abbreviations: N, number of patients; %, frequency.

**Table 5** Correlation among most common otoneurological symptoms in 30 patients with Friedreich's ataxia

SYMPTOMOLOGY	FRIEDREICH'S ATAXIA	
	N	%
Incoordination of movement	20	66.7
Gait imbalance	17	56.7
Dizziness	15	50.0

Abbreviations: N, number of patients; %, frequency.

**Table 6** Correlation between vestibular exam and most common otoneurological symptoms in 30 patients with Friedreich's ataxia

VESTIBULAR EXAM RESULT	INCOORDINATION OF MOVEMENT		GAIT IMBALANCE		DIZZINESS	
	N	%	N	%	N	%
Normal vestibular exam	–	0.0	1	3.4	1	3.4
Altered vestibular exam	20	66.7	16	53.3	14	46.6
Total	20	66.7	17	56.7	15	50.0

Abbreviations: N, number of patients; %, frequency.

Nacamagoe, Iwamoto, and Yoshida<sup>23</sup> reported that the combination of vestibular dysfunction in the presence of cerebellar atrophy can contribute significantly to the appearance of gait instability, which is part of the initial symptomatology of SCAs.

In this study, the videonystagmography (VNG) examination showed a higher prevalence of vestibular dysfunction (53.3%), as well as altered multiple-type semi-spontaneous nystagmus (40%), rotatory (36.7%), and optokinetic (33.4%) tests. Cerebellar vermis lesions cause ataxia of the upper limbs, head wobbling, dysmetria, and trembling eye movements, which is the body part that manifests electrical activity along the length of the eye muscles and neck.<sup>24</sup> The most common alterations in other studies<sup>11,22,24</sup> were the presence of positional nystagmus, irregular eye movement calibration, spontaneous rebound nystagmus, bi- and multi-directional semi-spontaneous nystagmus, abolition of optokinetic nystagmus, pendular tracking type IV nystagmus, hyporeflexia, absence of inhibitory effect of eye fixation, and Aubry signs in the Barany test. Among the damaged neuronal structures, the occurrence of vestibular dysfunction is known, but little is known about when and why it occurs. Takegoshi and Murofushi<sup>25</sup> report that spinocerebellar ataxia is one of the clinical entities in vestibular disorders.

Prim-Espada et al<sup>26</sup> performed an electrooculographic examination (EOG) on 51 patients diagnosed with genetic FA and observed alterations in saccadic movements for positional, spontaneous, and optokinetic nystagmus. The authors refer to suppression of the vestibular-ocular reflex (VOR) in all patients. Fahey et al<sup>27</sup> evaluated 20 patients with FA and observed that, despite presenting normal saccadic speed, extended latency was present. In addition, vestibular disorders were found with a marked reduction in the increase of the VOR. For Hocking, Fielding, and Corben,<sup>28</sup> altered saccadic latency can be useful as a marker of severity and progression in FA. Noval et al<sup>29</sup> performed eye examinations on 23 patients with FA and observed that visual acuity may decrease with disease progression, based on a small proportion of the patients without citing the percentage.

Zeigelboim et al<sup>11</sup> report that the loss of hair cells of the ampullary crests, as well as the decline in the number of nerve cells in the vestibular ganglion (Scarpa), degeneration of the otoliths, reduced labyrinthine blood flow, progressive depression of neural stability, and reduction in the compensation capacity of the vestibular-ocular and vestibulospinal reflexes all contribute to the reduction of speed in the eye tracking

motion, as well as rotatory and caloric hyporeactivity in the vestibular system, both peripheral and central, present in SCAs.

In this study, the result of the vestibular exam had a significant predominance of central vestibular dysfunction in 70% of patients. Ito et al<sup>22</sup> showed involvement of the central vestibular system and stressed the importance of vestibular evaluation in diseases affecting the posterior fossa. Prim-Espada et al<sup>26</sup> observed central alterations in the EOG exam in 72.5% of patients and Monday and Lemieux,<sup>30</sup> in 100% of cases via EOG exams. Fahey et al<sup>27</sup> and Kirkham et al<sup>31</sup> stressed that the range of alterations for eye movements suggest alterations in the brain stem, as well as the cortical and vestibular pathways.

In this study, we did not observe significance in the inter-correlation between the most evident symptoms (lack of coordination of movement, gait imbalance, and dizziness) for FA. We found no data that would challenge our findings.

It was evident that alterations in VNG are related to the severity of SCAs or the clinical stage of the disease.

The study emphasizes the importance of the vestibular evaluation for the topographic diagnosis of neurodegenerative diseases since, in most cases, the otoneurological symptoms present early and such information may aid in the choice of procedures to be performed in clinical and therapeutic monitoring.

## Conclusion

The most prevalent otoneurological symptoms were incoordination of movement, gait imbalance, and dizziness.

Alterations in the vestibular examination occurred in 90% of patients, located mainly in the caloric test, with a predominance of deficient central vestibular system dysfunction.

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