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Otoneurological findings in spinocerebellar ataxia

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Abstract

Objective: Describe findings observed in ENG of patients with spinocerebellar ataxias. **Method:** Forty-three patients were studied, and the following procedures were carried out: anamnesis, otorhinolaryngological and vestibular evaluation (ENG). **Results:** The clinical findings in the entire group of patients were: gait disturbances (83.72%), speech difficulties (48.83%), dizziness (41.86%) and dysphagia (39.53%). Vestibular examination disclosed abnormal caloric exam (83.71%) and saccadic movements (69.76%) with the highest rates of abnormality. The overall presence of alterations in vestibular tests was (90.70%), and the most frequent finding was central vestibular disorder in (74.42%) of patients. **Conclusion:** The study showed that alterations in ENG are related to the severity of SCAs or clinical stage of the disease. We emphasize the importance of studying the vestibular system concomitantly to clinical and genetic follow up.

Keywords: electronystagmographic, spinocerebellar ataxia, vestibular diseases.

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INTRODUCTION

Spinocerebellar ataxia is a disease belonging to a genetically and clinical heterogeneous group of neurodegenerative diseases characterized by progressive cerebellar ataxia[1]. They are classified as sensitive, frontal, vestibular and cerebellar, being this last one of interest for the present study[1].

Spinocerebellar ataxias (SCAs) have an average incidence of about 1 to 5 cases for 100.000 people[2]. The most common clinical manifestations are walking and appendicular ataxia (dysmetria, dysdiadochokinesia, intention tremor), dysarthria, nystagmus, ophthalmoplegia, dysphagia, pyramidal signs, lower motor neuron disease, cognitive dysfunction, epilepsy, visual disorders (pigmentary retinopathy), peripheral neuropathy, dementia and movement disorders (including parkinsonism, dystonia, myoclonia and chorea)[1,2-4]. SCAs may be divided according to genetic inheritance in: a) autosomal recessive ataxias; b) autosomal dominant ataxias; c) hereditary ataxias linked to chromosome "X" and d) inherited mitochondrial ataxias[5].

Its etiology is mostly mutations characterized by the presence of expanded trinucleotide CAG repeat unstable in the codified region of evaluated gene[2,5]. In Brazil, more specifically in the South region, a great number of families affected by SCA[2,5] has been identified. Machado-Joseph (DMJ) disease (SCA 3) is most common form of autosomal dominant ataxia identified in Brazil, in keeping with most epidemiologic world[2,5,6].

Different forms of SCAs has a variable geographic prevalence, e.g. SCA 2 has a high incidence in Cuba, India, England, France and United States; SCA 3, in Portugal, Brazil, Germany, Japan and China; SCA 6 has a high incidence in Japan, Australia and Germany; SCA 7, in Sweden, Finland, United States and China; and SCA 10, in Mexico and Brazil[1].

Electronystagmography (ENG) has allowed to sensitize the study of the labyrinth and its relationships with central nervous system (CNS), and allows differential topographical diagnosis of central and peripheral labyrinthopathies. The evaluation of the vestibular system is done through an otoneurological evaluation consisting of a set of procedures that allows a pathophysiological assessment of the vestibular system and its relation with the CNS with an emphasis in vestibulo-oculomotor, vestibulocerebellar, vestibulospinal and vestibuloproprioceptive-cervical interrelations[7].

Oculomotor abnormalities in patients with cerebellar dysfunction support the functional role of the cerebellum in maintenance of gaze eccentric portion, eye pursuit movements, modulation of the amplitude of saccadic movements and the visual suppression of caloric-induced nystagmus [8].

The aim of the present study is to describe the alterations observed in ENG in patients affected by spinocerebellar ataxias.

METHOD

This study was approved by the Committee of Institutional Ethics (number - 058/2008) and all patients gave an Informed Written Consent.

Forty-three patients (17 female and 26 male) were evaluated at the Neurology Service, Clinical Hospital, Federal University of Paraná, with established diagnosis of SCA (number of patients from each form: 12 SCA 3, 8 SCA 2, 1 SCA 4, 1 SCA 6, 1 SCA 7, 6 SCA 10), according to molecular genetics techniques with the use of PCR (polymerase chain reaction)[9-11]. Fourteen SCA patients do not have a genetic diagnosis yet. Their ages ranged between 18 and 70 years (mean, 41.6 $\pm$ 13.0) and the disease duration ranged between 1 and 15 years (mean, 7.9 $\pm$ 3.9), as shown in Table 1. Everyone was evaluated in the Sector of Otoneurology of the Tuiuti University of Paraná. Patients with significant visual, psychiatric, rheumatological, and musculoskeletal vulnerabilities or any abnormality that prevented completion of the evaluation, were excluded from the study.

The patients were submitted to the following procedures: **Anamnesis** - a questionnaire with emphasis on otoneurological signs and symptoms. **Otorhinolaryngological Evaluation** - to exclude any other unrelated physical abnormality that might interfere with the exam. Patients undertook a special diet, starting 72 hours before the otoneurological exams (avoid intake of coffee, any kind of soda or caffeinated tea, chocolate, smoking, or alcohol intake). Analgesics, tranquilizers, and antihistaminic and antivertigo medications were stopped during this period to minimize possible interferences with the test results. Three hours of fasting was recommended prior to the exam. **Vestibular Evaluation** - vestibular function evaluation consisted in several labyrinthine function and ocular tests. The first part of the evaluation was simply clinical and consisted of a systematic search for spontaneous, gaze, and positional nystagmus - Brandt and Daroff's maneuver[12]. The second part consisted of interpretation of the ENG test results, with objective register of variations in the corneoretinal potentials, captured by sensitive electrodes. The ENG test is composed of: calibration of ocular movements, search for spontaneous and gaze nystagmus, the oscillatory tracking test, optokinetic nystagmus search, and rotatory and caloric tests.

We performed ENG with a three-channel equipment (Berger Eletromedicina, model VN316, São Paulo, Brazil), rotating chair (Ferrante, model COD 14200, 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).

Table 1. Spinocerebellar ataxias (SCAs) and genetics aspects.

CASE	AGE (years)	GENDER	CLINICAL DIAGNOSIS	DURATION OF DISEASE (years)	CHROMOSSOME	GENE	MUTATION	PROTEIN
1	42	M	SCA3	12	14q32.1	ATAXIN3	CAG	Ataxin3
2	48	F	SCA3	15	14q32.1	ATAXIN3	CAG	Ataxin3
3	43	M	SCA3	12	14q32.1	ATAXIN3	CAG	Ataxin3
4	41	M	SCA3	8	14q32.1	ATAXIN3	CAG	Ataxin3
5	48	F	SCA3	10	14q32.1	ATAXIN3	CAG	Ataxin3
6	53	M	SCA3	13	14q32.1	ATAXIN3	CAG	Ataxin3
7	50	F	SCA3	8	14q32.1	ATAXIN3	CAG	Ataxin3
8	30	F	SCA3	9	14q32.1	ATAXIN3	CAG	Ataxin3
9	42	M	SCA3	10	14q32.1	ATAXIN3	CAG	Ataxin3
10	45	M	SCA3	15	14q32.1	ATAXIN3	CAG	Ataxin3
11	51	M	SCA3	7	14q32.1	ATAXIN3	CAG	Ataxin3
12	45	M	SCA3	3	14q32.1	ATAXIN3	CAG	Ataxin3
13	54	F	SCA2	11	12q24.1	ATAXIN2	CAG	Ataxin2
14	38	M	SCA2	8	12q24.1	ATAXIN2	CAG	Ataxin2
15	41	M	SCA2	12	12q24.1	ATAXIN2	CAG	Ataxin2
16	36	M	SCA2	3	12q24.1	ATAXIN2	CAG	Ataxin2
17	18	M	SCA2	2	12q24.1	ATAXIN2	CAG	Ataxin2
18	44	F	SCA2	3	12q24.1	ATAXIN2	CAG	Ataxin2
19	30	F	SCA2	10	12q24.1	ATAXIN2	CAG	Ataxin2
20	42	M	SCA2	12	12q24.1	ATAXIN2	CAG	Ataxin2
21	43	M	SCA4	5	16q24.qter	SCA4	PLEKHG4?	-
22	57	F	SCA6	5	19q13.1	CACNA1A	CAG	CACNA1A
23	47	F	SCA7	10	3p14.1	ATXN7	CAG	Ataxin7
24	49	F	SCA10	6	22q13.3	ATXN10	ATTCT	Ataxin10
25	46	M	SCA10	10	22q13.3	ATXN10	ATTCT	Ataxin10
26	27	F	SCA10	3	22q13.3	ATXN10	ATTCT	Ataxin10
27	70	M	SCA10	13	22q13.3	ATXNA0	ATTCT	Ataxin10
28	54	M	SCA10	11	22q13.3	ATXN10	ATTCT	Ataxin10
29	56	F	SCA10	12	22q13.3	ATXN10	ATTCT	Ataxin10
30	24	M	n.d.	2	-	-	-	-
31	27	M	n.d.	7	-	-	-	-
32	20	M	n.d.	1	-	-	-	-
33	32	M	n.d.	5	-	-	-	-
34	22	M	n.d.	8	-	-	-	-
35	22	M	n.d.	7	-	-	-	-
36	62	M	n.d.	3	-	-	-	-
37	66	M	n.d.	12	-	-	-	-
38	18	F	n.d.	4	-	-	-	-
39	23	M	n.d.	1	-	-	-	-
40	37	F	n.d.	9	-	-	-	-
41	48	F	n.d.	8	-	-	-	-
42	48	F	n.d.	8	-	-	-	-
43	51	F	n.d.	7	-	-	-	-

n.d.: not determined; SCA3: spinocerebellar ataxia type 3; SCA2: spinocerebellar ataxia type 2; SCA4: spinocerebellar ataxia type 4; SCA7: spinocerebellar ataxia type 7; SCA6: spinocerebellar ataxia type 6; SCA10: spinocerebellar ataxia type 10; M: male; F: female.

We compared the results with normal control data, obtained from epidemiological studies for the Brazilian population[13-15]. The criteria used to analyze each test as well as to distinguish central from peripheral vestibulopathy is shown in Table 2. We calculated Difference-of-Proportion test using a significance level of 5% ($p < .05$).

RESULTS

The most common complaints in anamnesis were gait disturbances (83.72%), speech difficulties (48.83%), dizziness (41.86%) and dysphagia (39.53%) (Table 3).

In the evaluation of vestibular function, caloric test, saccadic movements, positional, spontaneous, gaze nystagmus, optokinetic and rotatory nystagmus the finding in SCAs are depicted in Table 4.

Among the abnormal tests results in all SCAs, the commonest was the caloric test (83.71%), demonstrating a labyrinth hypofunction, in saccadic movements (69.76%), representing difficulty in pursuit movements, gaze nystagmus (48.82%), and in rotatory test (46.51%), which demonstrates an absent response of the lateral semicircular, anterior and posterior ducts (Table 4).

The difference-of-proportion test revealed a significant difference between bilateral vestibular hyporeflexia and absent rotatory nystagmus ($p = 0.0050$*) and a significant difference between dysmetric saccades and absent rotatory nystagmus ($p = 0.0317$*).

We verified that the ratio of bilateral vestibular hyporeflexia and dysmetric saccades were more prevalent and significant when compared to controls.

Table 2. 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 (<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 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 19 degrees/sec Relative values: Labyrinth preponderance <33% Nystagmus directional preponderance <22%	Absolute value: <2 degrees/sec (hyporeflexia), >19 degrees/sec (hyperreflexia) and areflexia Relative values: Labyrinth preponderance >33% Nystagmus directional preponderance >22% (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

Source: Based on Padovan and Pansini (14), Mangabeira-Albernaz et al. (15) and Ganança et al. (16).

Table 3. Frequency of symptoms of 43 patients with SCA.

SYMPTOMS	NUMBER OF PATIENTS	FREQUENCY (%)
Gait disturbances	36	83.72
Speech difficulties	21	48.83
Dizziness	18	41.86
Dysphagia	17	39.53
Voice alteration	15	34.88
Hearing loss	12	27.90
Headache	11	25.58
Falls	11	25.58
Diplopia	10	23.25
Extremities tingling	7	16.27
Anxiety	6	13.95
Blurred vision	5	11.62
Tremor	5	11.62
Pain, irradiated to shoulder, arm	5	11.62
Insomnia	5	11.62
Depression	5	11.62
Pain, difficulty in neck movement	4	9.30
Migraine	4	9.30
Tinnitus	4	9.30
Fatigue	3	6.97

SCA: spinocerebellar ataxia.

Regarding the results of vestibular examination, a higher incidence of central vestibular abnormalities was observed (74.42%) and more common in males, as show Tables 5 and 6.

The difference-of-proportion test revealed a significant difference between abnormal and normal exams (p = 0.0000*) and between central and peripheral vestibular disorders (p = 0.0000*).

DISCUSSION

The symptoms more commonly reported by SCA patients were also observed by other authors[1,2-4]. Due to the multiplicity of clinical forms, different manifestations may occur during the evolution of the disease.

Nacamagoe et al.[16] reported that the combination of vestibular dysfunction with the presence of cerebellar atrophy can contribute significantly to the emergence of instability during walking, which is part of the initial symptoms of SCA.

Regarding ENG findings, a high prevalence of vestibular hypofunction was observed (83.71%), followed by alterations of saccadic movements (69.76%), of gaze nystagmus (48.82%) and in rotatory test (46.51%). Injuries of the cerebellar vermis cause ataxia of the superior limbs, head titubation, dysmetria and tremor of the ocular movements and this is the part that manifests electric activity in the extension of ocular muscles and the neck. There is evidence showing that injuries in the cerebellar vermis cause vertical dysmetria whereas more lateral or paravermian injuries cause horizontal dysmetria. Moreover, anterior vermal lesions are related to upper gaze dysmetria, whereas down gaze dysmetria is usually observed in posterior vermal lesions[17]. The most common alterations reported in other studies were the presence of positional nystagmus, irregular calibration of ocular movements, spontaneous rebound and multiple gaze nystagmus, optokinetic abnormality, pendular tracking,

Table 4. Frequency of abnormal findings in the vestibular evaluation in 43 patients with SCA.

FINDINGS	SCA 2		SCA 3		SCA 4		SCA 6		SCA 7		SCA 10		INDF		SCAT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Bilateral vestibular hyporeflexia	4	50.00	11	91.66	-	0.00	1	100.00	1	100.00	4	66.66	12	85.71	33	76.74*
Rotative nystagmus absent	4	50.00	7	58.33	-	0.00	-	0.00	1	100.00	1	16.66	7	50.00	20	46.51*
Spontaneos nystagmus with open eyes	-	0.00	-	0.00	-	0.00	1	100.00	-	0.00	-	0.00	-	0.00	1	2.32
Dismetric saccades	6	75.00	7	58.33	-	0.00	1	100.00	1	100.00	5	83.33	10	71.42	30	69.76*
Gaze nystagmus unidirectional	2	25.00	1	8.33	-	0.00	-	0.00	-	0.00	-	0.00	-	0.00	3	6.97
Gaze nystagmus multiple	-	0.00	4	33.33	-	0.00	1	100.00	1	100.00	5	83.33	3	21.42	14	32.55
Optokinetic nystagmus asymmetrical	2	25.00	7	58.33	-	0.00	-	0.00	1	100.00	1	16.66	2	14.28	13	30.23
Gaze nystagmus bidirectional	-	0.00	1	8.33	-	0.00	-	0.00	-	0.00	-	0.00	3	21.42	4	9.30
Unilateral vestibular hyporeflexia	1	12.50	-	0.00	-	0.00	-	0.00	-	0.00	-	0.00	2	14.28	3	6.97
Positional vertigo and/or nystagmus	1	12.50	-	0.00	-	0.00	-	0.00	-	0.00	-	0.00	-	0.00	1	2.32

SCA: spinocerebellar ataxia; INDF: indefinite; SCAT: total spinocerebellar ataxia; n: number of patients; %: frequency.
p< .05; depicting a significant proportion. The results indicating a significant difference between the bilateral vestibular hyporeflexia and rotative nystagmus absent, (p = 0,0050) and dysmetric saccades and rotative nystagmus absent (p = 0,0317*).

Table 5. Frequency of results in the vestibular evaluation in 43 patients with SCA.

VESTIBULAR EXAM	SCA 2		SCA 3		SCA 4		SCA 6		SCA 7		SCA 10		UNDF		SCAT	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Central vestibular disorders	5	62.50	9	75.00	-	0.00	1	100.00	1	100.00	5	83.33	11	78.58	32	74.42*
Peripheral vestibular disorders	1	12.50	3	25.00	-	0.00	-	0.00	-	0.00	-	0.00	3	21.42	7	16.28
Normal vestibular exam	2	25.00	-	0.00	1	100.00	-	0.00	-	0.00	1	16.67	-	0.00	4	9.30

SCA: spinocerebellar ataxia; UNDF: undefined; SCAT: total spinocerebellar ataxia; n: number of patients; %: frequency.
*p< .05; depicting a significant proportion.
The results indicate a significant difference between altered and normal exams (p = 0,0000*) and between central vestibular disorders and peripheral vestibular disorders rotative nystagmus absent, (p = 0,0000*).

Table 6. Distribution of the 43 patients according to gender and results of vestibular exam.

EXAM RESULT	Male		Female		Total	
	n	%	n	%	n	%
Abnormal	24	92.30	15	88.23	39	90.70
Normal	2	7.70	2	11.77	4	9.30
Total	26	100.00	17	100.00	43	100.00

n: number of patients; %: frequency.

vestibular hypofunction and absence of the inhibiting effect of ocular, what is in keeping with our findings[7,17].

Amongst the damaged neuronal structures, it is known of the occurrence of vestibular hypofunction, but little is known regarding when and why it occurs[18,19]. Yoshizawa et al. [20] evaluated two patients with SCA 3 with genetic at the beginning of symptoms, that is, one year in case 1 and three years in case 2. They observed that in both cases caloric tests there was no response.

Yoshizawa et al. [21] reported a reduction in the size of the pontine tegmentum and medulla seen at MRI scans, where vestibular nuclei, prepositus perihypoglossal (nucleus intercalates, nucleus prepositus, and the nucleus of Roller – all located in the gray matter of the medulla) and neurons of the paramedian tract related with vestibular system are all located**.** Early degeneration of these structures may lead to an atrophy of the brainstem.

Zeigelboim et al.[7] showed that the loss of ciliated cells in the ampullary cupula and maculae, decreased number of neuronal bodies of the vestibular ganglion (Scarpa's), degeneration of otoliths, reduction of labyrinth blood flow, progressive depression of neural stability, reduction in the capacity of the compensation from vestibulo-ocular and vestibulospinal reflexes all these changes contribute to the reduction of the speed of the pursuit movements and rotational and caloric hyporeactivity of the central and peripheral vestibular system which are typically present in SCAs.

MRI examination in SCA 3 patients reveals cerebellar atrophy, with or without brainstem involvement (olivopontocerebellar atrophy)[2,9,10,22].

Anatomopathological studies[23] of the vestibular complex and the association of its fiber bundles in four patients with SCA 3 revealed that the five nuclei of the vestibular complex (interstitial, lateral, medial, inferior and superior vestibular nuclei have neurodegenerative changes caused by the disease, demonstrating that all the associated fiber tracts (ascending tract of Deiters, juxtarestiform body, lateral and medial vestibulospinal tracts, medial longitudinal fasciculus, cranial vestibular contest portion of the eighth nerve), suffer widespread neuronal loss causing atrophy and demyelination of the structures. These lesions can explain the alterations of the brainstem, postural instability with disequilibrium, oculomotor deficits (impaired optokinetic nystagmus, slow saccadic eye movements and absent caloric response) and presence of pathological vestibulo-ocular reflex (VOR)[24].

SCA 2 is characterized by cerebellar atrophy with a loss of Purkinje and granular cells, olivary neurons, substantia nigra and cells in the anterior horn of the spinal cord[9,25]. Neurological examination showed slow saccades, saccadic smooth pursuit, scanning speech and ataxia[26].

SCA 4 is a rare kind of ataxia characterized by cerebellar ataxia association to peripheral neuropathy and involvement of the pyramidal tract. Neuropathological studies revealed a reduction of Purkinje and ganglionar cells of the dorsal and the dorsal column of spinal cord[27]. Hellenbroichet al.[28] in a post-mortem study of a SCA 4 patient report severe neuronal loss in the Purkinje cell layer of the cerebellum, in the cerebellar fastigial nucleus, in the red, trochlear, lateral vestibular, and lateral reticular nuclei, the reticulotegmental nucleus of the pons, and the nucleus of Roller. The functional role of the affected nuclei and related fiber bundles may explain the symptoms that occur during the course of the disease (ataxia, dysarthria, somatosensory deficit, diplopia, gaze-evoked nystagmus, auditory impairments, altered brainstem auditory evoked potentials, saccadic smooth pursuits, impaired somatosensory functions in the face and dysphagia [28].

SCA 6 studies show a reduction of Purkinje cells and also gliosis of the inferior olivary complex. Ishikawa et al.[29] reported that SCA 6 patients present intense vertiginous episodes that precede the beginning of ataxia, the presence of spontaneous and gaze-evoked downbeat nystagmus as the predominant signs[30].

SCA 7 presents from the neuropathological point of view of a olivopontocerebellar degeneration associated to a reduction of ganglion cells of the retina and pigmentary macular dystrophy[31]. There are also pyramidal signals, slow ophthalmoplegia, parkinsonism and saccadic movements in particular[10,25].

SCA 10 studies demonstrate the presence of pan-cerebellar atrophy, without abnormalities in other regions[32]. There is also the presence of nystagmus with changeable direction and type[1].

SCAs are genotypically and phenotypically very heterogeneous. Various authors have suggested that detailed analysis of abnormal eye movements may help to identify some SCAs forms (types 2, 3 and 6). The mains abnormalities, such as changes in the amplitude and speed of saccadic movements, the presence of gaze-evoked nystagmus and impairment of de VOR, are common in certain types of SCA[25].

Degenerative diseases may produce a variety of abnormal findings in ENG. Tsutsumi et al. [33] evaluated 72 patients with cerebral degeneration and observed a high incidence of saccadic pursuit and upward ocular dysmetria. They also observed moderate incidences of horizontal ocular dysmetria, gaze-evoked and rebound nystagmus, vertical positioning nystagmus and impaired visual suppression appeared to reflect the degree of dysfunction, while optokinetic nystagmus seems to reflect both the presence of disease and its severity.

The study showed that alterations in ENG are related to the severity of SCAs or clinical stage of the disease. We emphasize the importance of studying the vestibular system concomitantly to clinical and genetic follow up.

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