

Vestibular Findings in Relapsing, Remitting Multiple Sclerosis: A Study of Thirty Patients

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Abstract: Our objective was to describe vestibular abnormalities in patients with relapsing and remitting multiple sclerosis. Thirty patients (6 men and 24 women) between 27 and 64 years of age underwent neurological and otolaryngological examinations, complete anamnesis, and electronystagmography. Patients with psychological or oculomotor paresis (or both), internuclear ophthalmoparesis, severe visual disturbances, or locomotion restrictions were excluded. The difference-of-proportion test was used to compare affected patients with controls, with a significance level of 5%. Vestibular alterations were found in 26 (86%) of the evaluated patients, from which 25 presented peripheral etiology and only 1 presented a problem of central origin. There was a prevalence of bilateral peripheral irritative vestibulopathy (20%), followed by bilateral peripheral deficit vestibulopathy (20%) and left peripheral deficit vestibulopathy (17%). The high incidence of vestibular disorders observed in this study indicates that this population might benefit from specific rehabilitation programs. Studies with larger samples are still required and may contribute to the understanding of this pathology.

Key Words: multiple sclerosis; vertigo; vestibular diseases; vestibular function tests

Multiple sclerosis (MS) is an inflammatory autoimmune disorder of the central nervous system and a common cause of neurological disability in young adults. As with all complex traits, the disorder results from gene susceptibility and environmental factor interplay [1,2]. The symptoms and signs of relapsing and remitting multiple sclerosis (RRMS) typically evolve over a period of several days, stabilize, and then often diminish either spontaneously or in response to corticosteroid administration. RRMS onset is typically observed in the second or third decade of life,

predominantly in females (2:1). First signs are usually related to sensory disturbances, unilateral optic neuritis, diplopia (e.g., internuclear ophthalmoplegia), Lhermitte's sign (trunk and limb paresthesia evoked by neck flexion), limb weakness, clumsiness, gait ataxia, and neurogenic symptoms affecting the bladder and bowels. Many patients describe fatigue, worse in the afternoon, and fever. The diagnosis is based on clinical and laboratory criteria described by Poser and McDonald et al. [3–5].

Vertigo, balance disorders, and the presence of nystagmus are often mentioned as early manifestations of RRMS [6,7]. Positional nystagmus of different types—rotatory, vertical, semispontaneous, and caloric hyperreflexia—may also be observed [8]. Guillain [9] reported the presence of the classic Charcot triad (nystagmus, dysarthria, and intention tremor), and Velter [10] also observed the vertigo, plus presence of tingling sensation in legs and arms, muscular weakness, and tiredness. As regards to hearing function, many studies reported hearing loss as an unusual symptom [9,11–16].

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Unfortunately, investigations on ocular alterations and epidemiological studies concerning the prevalence of MS are still rare in Brazil. The most recent data on this subject were published by Callegaro et al. [17], who reported the prevalence of 5/100,000 inhabitants of São Paulo, having investigated a population of 9,380,000 in 1997. The patients were classified according to the criteria of Poser et al. [3], and only those with defined MS were registered.

As electronystagmography (ENG) may be useful to the early diagnosis of MS [6] and considering the scarcity of studies using regional standard values, this study intends to describe the vestibular abnormalities observed in 30 patients with RRMS in comparison with those in a control group.

PATIENTS AND METHOD

We evaluated 30 patients (6 men and 24 women) with a final diagnosis of RRMS, according to Poser's and McDonald's criteria [3,5]. We registered the patients randomly selected for the study at a reference center for diagnosis and treatment of MS (Institute of Neurology of Curitiba). Their ages ranged between 27 and 64 years (mean, 42.23; standard deviation [SD], 9.68).

We performed the evaluation regardless of the type, period of treatment, or diagnosis date, after receiving a patient's formal agreement (signing of an informed consent form) approved by the local ethics committee.

All patients underwent a visual evoked potential exam and brain and cervical cord magnetic resonance imaging scans [5] and were classified according to the Kurtzke scale [18,19]. After a complete neurological exam, patients with psychological or oculomotor paresis (or both), internuclear ophthalmoparesis, or other severe visual disturbances were excluded. Laboratory exams were composed of specific analyses to detect infectious and autoimmune diseases; analysis of the cerebrospinal fluid; immunoelectrophoresis for detection of oligoclonal bands; and serological tests (VDRL and HTLV-1). Patients presenting results that did not match the Poser and McDonald criteria for RRMS were excluded.

A questionnaire to obtain otoneurological symptoms and personal and family information was applied (protocol developed by the Department of Otoneurology, University of Tuiuti of Parana). 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 inter-

ferences 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.

Clinical Evaluation

The search for positional nystagmus and vertigo was verified through Brandt and Daroff's maneuver [20]. 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, 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 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).

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: $x = 2y.tg5$ degrees, where x is the distance between the targets and y is the distance between the patient and the target and tg (tangent of 5). 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 velocity of nystagmus 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 maximum slow-component angular velocity (MSCAV) of nystagmus were evaluated. To calculate the directional preponderance, we used the Jongkees formula [21] detailed below.

$$DP = [(MSCAV_{ccw} - MSCAV_{cw}) / (MSCAV_{ccw} + MSCAV_{cw})] \times 100\%$$

where

DP = directional preponderance

MSCV_{ccw} = maximum slow-component angular velocity, counterclockwise

MSCV_{cw} = maximum slow-component angular velocity, clockwise

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 [22]. The air stimuli were set at the temperatures of 42°C, 18°C, and 10°C, lasting 80 seconds each. Records were registered with open and closed eyes to note IEOF, direction, MSC absolute values, and correlation between directional preponderance and post-caloric nystagmus direction. Normal absolute values are within 2 degrees and 19 degrees per second, whereas normal relative values are lower than 33% for labyrinth preponderance and less than 22% for nystagmus directional preponderance.

We compared results with normal standards, obtained from epidemiological studies for the Brazilian population [23–25]. 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 and is rather a negative diagnosis. The difference-of-proportion test searched for a statistically significant difference in ENG results, comparing the affected patients with those in the control group ($p < .05$).

RESULTS

Table 2 shows the patients' complaints at the time of examination. We found no significant alteration regarding position nystagmus, gaze nystagmus, calibration of the ocular movements, oscillatory tracking test, optokinetic nystagmus, or rotation test.

The spontaneous nystagmus was altered in one patient (3.3%). The nystagmus was horizontal, to the right, with an angular velocity of 14 degrees per second, indicating central vestibulopathy.

Alterations of vestibular function were found in 26 patients (86.7%; Table 3), all in the peripheral vestibular apparatus and with a higher prevalence in female patients (80%). In this study, vestibular exam results were altered in 26 patients (86.7%); most alterations were found in the peripheral vestibular system (83.4%). This finding may be related to the initial stage of the disease.

From an otoneurological point of view, two distinct situations may be observed regarding RRMS: (1) in the initial stage of the disease, vertigo is an early symptom, and central impairments may be rare at ENG; whereas (2) in the advanced stage of the disease, vertigo is reported in 50% of the cases and central alterations at ENG are more frequent [13].

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 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), >19 degrees/sec (hyperreflexia) and areflexia Relative values: Labyrinth preponderance >33% Nystagmus directional preponderance >22% (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 Ganança et al. [25], Mangabeira-Albernaz et al. [24], and Padovan and Pansini [23].

Table 2. Incidence and Frequency of Complaints

Complaints	Incidence	Frequency (%)
Dizziness	18	15.7
Extremities tingling	9	7.8
Headache	9	7.8
Gait disturbances	9	7.8
Anxiety	8	7.0
Fatigue	8	7.0
Pain, difficulty in neck movement	6	5.2
Depression	6	5.2
Blurred vision	6	5.2
Tremor	5	4.3
Voice alteration	5	4.3
Sleeping disorders	5	4.3
Diplopia	4	3.5
Neck clicking	4	3.5
Pain irradiated to shoulder, arm	4	3.5
Facial tingling	3	2.6
Facial palsy	3	2.6
Speech difficulties	3	2.6

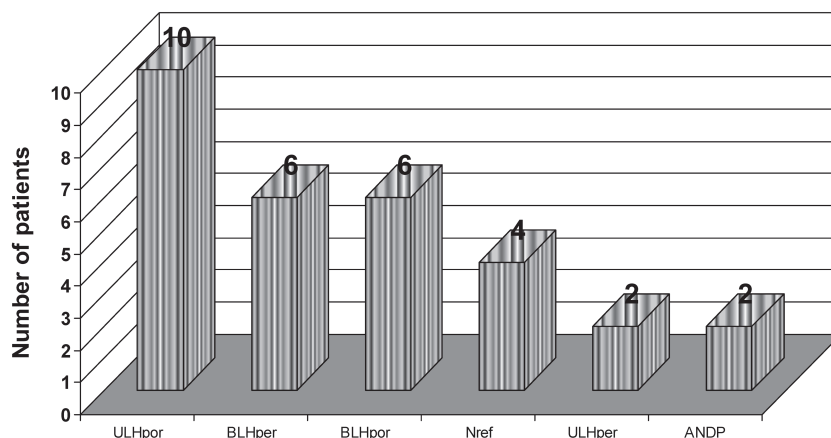
The difference-of-proportion test revealed a significant difference between altered and normal ratio related to gender ($p < .05$). Figure 1 shows the incidence of abnormal findings at ENG, and Figure 2 shows the vestibular test conclusions.

Table 3. Distribution of Patients According to Gender and Results of Vestibular Test

Test Result	Gender		Total n (%)
	Male n (%)	Female n (%)	
Abnormal	5 (16.7)*	21 (70)*	26 (86.7)
Normal	1 (3.3)	3 (10)	4 (13.3)
Total	6 (20)	24 (80)	30 (100)

* $p = .05$. (The results indicate a significant difference between the genders in the altered group.)

Figure 1. Frequency of caloric test results: absolute and relative analysis. (*ANDP* = asymmetrical nystagmus directional preponderance; *BLHper* = bilateral labyrinth hyperreflexia; *BLHpor* = bilateral labyrinth hyporeflexia; *Nref* = normoreflexia; *ULHper* = unilateral labyrinth hyperreflexia; *ULHpor* = unilateral labyrinth hyporeflexia.)



DISCUSSION

We could not identify any pathognomonic set of vestibular findings in patients with MS. MS may present quite variable clinical manifestations during its clinical course and may involve several peripheral or central structures of the vestibular apparatus. Equilibrium disorder is the most frequent symptom when the vestibulo-oculomotor system is affected [13,26].

Anamnesis findings included motor, sensory, vestibular, and psychological symptoms, imbalance, dizziness, tingling sensation of hands and feet, and headache [14, 27,28]. Other authors also report several degrees of sensory and motor disorders [9,13,29,30]. Symptoms vary individually and may evolve along with the disease. Our study found a major prevalence in women (80%) in accordance with other authors [6,13,14,16,30–32]. Conversely, several authors reported an equal incidence for both genders [29,33–35]. Findings from this study revealed alterations in the spontaneous nystagmus search and in the caloric test.

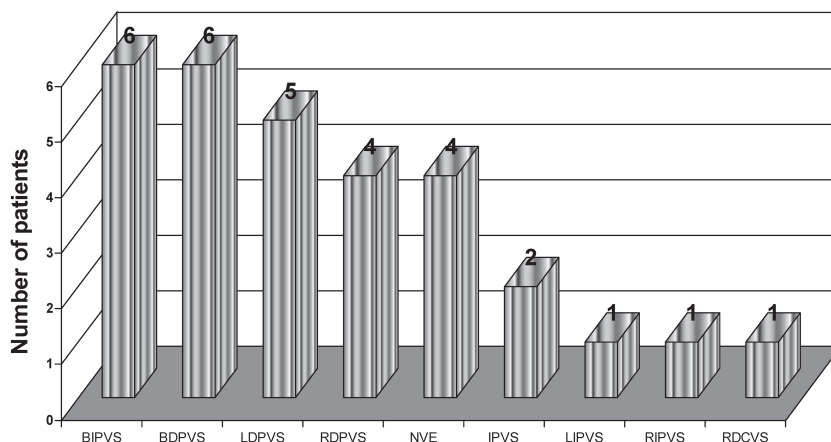
Presence of horizontal spontaneous nystagmus (with open eyes and slow-component velocity of 14 degrees)

and absence of inhibiting effect are also reported in the literature [6,36,37]. In 1983, Mangabeira-Albernaz et al. [13] posited that spontaneous nystagmus is one of the most frequent signs of MS. The most frequent types of nystagmus are vertical, diagonal, horizontal, rotatory, and dissociated. These findings are supported by Cipparrone et al. [35].

No alteration was observed in this study regarding gaze nystagmus search, oscillatory tracking, and optokinetic and rotatory tests. The literature corroborates that patients may present alterations of the saccadic movements, gaze nystagmus, oscillatory track type III or IV that is pathognomonic for central alteration, asymmetrical optokinetic nystagmus, and rotatory test with absence of diagonal nystagmus under stimulation of the vertical semicircular ducts and decruitment [6,13,16,36,38–40].

Results from this study revealed alterations in the caloric test results, with unilateral and bilateral labyrinth hyporeflexia and bilateral labyrinth hyperreflexia. Cipparrone et al. [35] reported a bilateral hyperreflexia in 36% of cases. Mangabeira-Albernaz et al. [13] found 25% of disorders in this exam, evincing bilateral hyperreflexia and absence of inhibiting effect.

Figure 2. Distribution and frequency of the different types of vestibulopathy. (*BDPVS* = bilateral deficient peripheral vestibular syndrome; *BIPVS* = bilateral irritative peripheral vestibular syndrome; *IPVS* = irritative peripheral vestibular syndrome; *LDPVS* = left deficient peripheral vestibular syndrome; *LIPVS* = left irritative peripheral vestibular syndrome; *NVE* = normal vestibular exam; *RDCVS* = right deficient central vestibular syndrome; *RDPVS* = right deficient peripheral vestibular syndrome; *RIPVS* = right irritative peripheral vestibular syndrome.)



Our results showed a high incidence of bilateral peripheral irritative vestibulopathy followed by left peripheral hypofunctional vestibulopathy and bilateral deficit peripheral vestibulopathy. These findings were also observed in other reports [7,13,28,35,41]. More recently, in a Brazilian survey, Tomaz et al. [28] found 60% of MS patients with irritative vestibulopathy and 13.4% with central vestibular disorders. Prosser et al. [42] observed the presence of both hyperreflexia and hyporeflexia in MS patients submitted to caloric stimulation. Central vestibular structures were spared in our patients. Follow-up studies of the vestibular function in MS patients may provide more details that can explain these findings. Studies on the vestibular function of patients with RRMS usually involve biases, such as the developmental stage of the disease, the duration and type of treatment, frequency of the crises, and severity of global impairment.

According to Herdman [43], vestibular rehabilitation acts on the vestibular system through the repetition of specific physical exercises that activate central neuroplastic mechanisms to achieve adaptive compensation of the impaired functions. The success of otoneurological therapy depends on the accurate diagnosis and detection of the lesion, including its location and etiology. The most common treatment choices for vestibular dysfunctions are drug administration, surgical procedures, and vestibular rehabilitation.

Of the 30 patients evaluated in our study, 15 are enrolled in vestibular rehabilitation as an adjuvant treatment, following the vestibular rehabilitation protocols described by Cawthorne [44] and Cooksey [45], with positive results.

CONCLUSION

This study is an innovative work in Brazil, developed by a multidisciplinary team involving professionals of different areas (otorhinolaryngologist, neurologists, and speech-language pathologists). Positive results were observed during the practice of the exercises in group sessions, indicating that this therapeutic method may be extremely valuable for increasing motivation, socialization, and interaction among these patients. We reinforce the scarcity of articles related to this topic, which brings up the importance of this study and of the otoneurological regular follow-ups, based on the positive results obtained for this population.

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