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Ocular motor impairment in early-stage multiple sclerosis: a video-oculography assessment

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Abstract

Background Eye movement disorders in multiple sclerosis (MS) are frequently misdiagnosed and frequently overlooked during clinical examinations. Even at a preclinical state, these defects frequently cause impairment and weariness.

Methods We conducted a cross-sectional observational study including 20 individuals with a confirmed MS diagnosis. The inclusion criteria were an EDSS score of 4 or less and a 6-month interval between the last relapse and enrolment. As part of the MS assessment, a routine ORL, neurology exam, eye exam, assessment of eye movement using Ulmer's videonystagmography battery tests, and routine brain MRI were performed on the patient.

Results A total of 75% of the patients in our series are female, with a mean age of 39 years and a range of 24 to 59 years. The average age of MS onset is 32 years. The relapsing-remitting type of multiple sclerosis (RRMS) accounts for 95% of all cases. There is only a single case of secondary progressive disease course (SPMS). Principal VNG manifestations are related to subclinical eye movements abnormalities. Rotatory vertigo caused by vestibular dysfunction was less prevalent than other balance disorders. There were found to be two types of nystagmus: pendular and central positional nystagmus.

Discussion and conclusion VNG is sensitive for detecting vestibular system dysfunction in MS patients. It is also beneficial for diagnosing subtle eye movement abnormalities that are usually overlooked.

Keywords Multiple sclerosis, Videonystagmography, Eye movement abnormality, Nystagmus, Vestibular syndrome

Background

Multiple sclerosis (MS) is the leading nontraumatic cause of motor impairment in youth [1]. It affects the central nervous system's white matter. This condition is characterized by recurring episodes of neurological deficits that occur between periods of complete or incomplete recovery. Three main clinical forms are described: relapsing remitting disease course (RRMS), which accounts for 80% of patients; primary progressive disease course (PPMS), which accounts for 15 to 20% of all patients; and secondary progressive disease course (SPMS), which impacts 60% of the patients after 10 to 15 years of disease evolution [2]. The Expanded Disability Status Scale (EDSS) is a recognized approach for quantifying impairment in MS [3]. Disability due to oculomotor impairment is reported in 60 to 80% [4–6]. This may be a result of involvement of central ocular motor or central vestibular pathways. Although

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vestibular involvement in MS is very common, MS patients seldom report subjective vertigo; rather, balance abnormalities are more common [7–9]. Our objective is to investigate eye movement problems in MS and identify any subtle impairment. These signs are frequently underappreciated and a significant cause of impairment in MS patients.

Methods

We conducted a cross-sectional observational research including 20 patients having a confirmed MS diagnosis. The inclusion criteria were an EDSS score of 4 or less (Table 1) and a 6-month interval between the last relapse and enrolment. The protocol for the study was approved by our ethic committee.

As part of the MS assessment, a routine ORL, neurology exam, eye exam, audiology tests, assessment of eye movement utilizing Ulmer's videonystagmography battery tests, and routine brain MRI have been done on the patients.

ORL examination consists of regular upper aerodigestive tract examination, audiovestibular, and cranial nerve evaluations.

The neurology examination involves assessments of global and segmental motility, cerebellar function, and all sensory modalities.

Evaluation of visual acuity, visual field, and global eye motility is included in the eye examination.

Videonystagmography (VNG) permits the recording of horizontal and vertical eye movements in real time on a graph during regular eye examinations and evaluations of oculovestibular pathways.

VNG employs a specialized pair of goggles with detachable and clippable eye cover and a camera to record eye movements. Due to the infrared camera's integration, recording is feasible with vision allowed or with vision denied (Fig. 1).

Eye movements such as pursuit, saccades, and optokinetic responses that require participation of vision can be studied when no eye cover is present during recording. Using eye coverings enables the recording of eye movement in the dark which allows the study of spontaneous and induced nystagmus, as well as gaze nystagmus, providing crucial information on the functioning of peripheral vestibulo-ocular pathways.

VNG monocular assessment tests performed were as follows:

Table 1 Expanded Disability Status Scale (EDSS) [10]

Score	Description
0	Normal neurological exam, no disability in any FS
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS or mild disability in three or four FS. No impairment to walking
3.5	Moderate disability in one FS and more than minimal disability in several others. No impairment to walking
4.0	Significant disability but self-sufficient and up and about some 12 h a day. Able to walk without aid or rest for 500 m
4.5	Significant disability but up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance. Able to walk without aid or rest for 300 m
5.0	Disability severe enough to impair full daily activities and ability to work a full day without special provisions. Able to walk without aid or rest for 200 m
5.5	Disability severe enough to prelude full daily activities. Able to walk without aid or rest for 100 m
6.0	Requires a walking aid — cane, crutch, etc. — to walk about 100 m without resting
6.5	Requires two walking aids — pair of canes, crutches, etc. — to walk about 20m without resting
7.0	Unable to walk beyond approximately 5 m even with aid. Essentially restricted to wheelchair, though wheels self in standard wheelchair and transfers alone. Up and about in wheelchair some 12 h a day
7.5	Unable to take more than a few steps. Restricted to wheelchair and may need aid in transferring. Can wheel self but cannot carry on in standard wheelchair for a full day and may require a motorized wheelchair
8.0	Essentially restricted to bed or chair or pushed in wheelchair. May be out of bed itself much of the day. Retains many self-care functions. Generally, has effective use of arms
8.5	Essentially restricted to bed much of day. Has some effective use of arms retains some self-care functions
9.0	Confined to bed. Can still communicate and eat
9.5	Confined to bed and totally dependent. Unable to communicate effectively or eat/swallow
10.0	Death due to MS

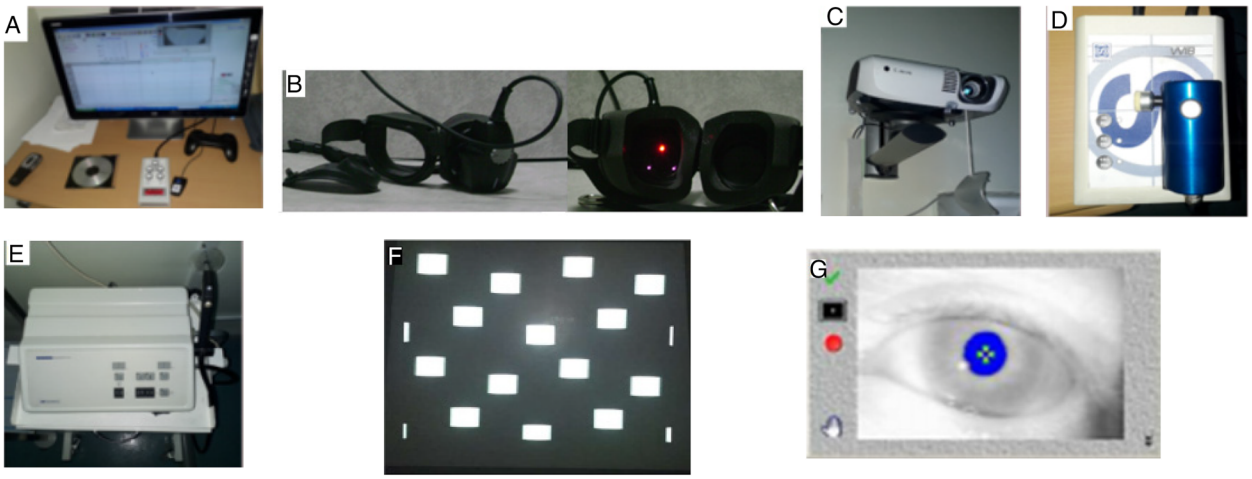

Fig. 1 VNG sittings

- Eye movements recording includes saccades, pendular tracking, and optokinetic nystagmus
- The accuracy, latency, and peak velocity metrics were used to evaluate saccades as follows:
- Saccades latency or "reaction time" is the time interval between the target's movement and the initiation of the first saccade toward the new position; it is measured in milliseconds.
- Maximum velocity or maximum velocity saccades: for an amplitude of 40°, the maximum velocity reachable is 400°/s.
- Precision, or the accuracy of saccades, is the ratio of amplitudes between the refixation saccade and the angle of deflection of the target. The usual range for this ratio is between 70 and 100%.
- Tracking test: Typically, the resulting curve is a sinusoid. Saccadic tracking is a result of decreased gain which suggests central dysfunction.
- The gain of the optokinetic response is derived from the accumulated slow phases of optokinetic nystagmus (OKN). A low gain suggests a brainstem lesion.

In addition, vestibulo-ocular pathways were evaluated by recording spontaneous nystagmus, gaze-evoked nystagmus, positional nystagmus, and caloric testing.

Results

Seventy-five percent of the patients in our series are female, with a mean age of 39 years and a range of 24 to 59 years. The average age of MS onset is 32 years. The relapsing-remitting type of multiple sclerosis (RRMS) accounts for 95% of all cases. There is only a single instance of secondary progressive multiple sclerosis (SPMS).

In 35% of cases (7 instances), motor disorders are the predominant first symptoms; balance disorders (vertigo and imbalance) are present in 30% of cases (6 cases). Four patients (20%) had visual and/or ocular motor problems, while three patients (15%) exhibited a multisymptomatic first episode involving visual, vestibular, and sensory symptoms. Thirty percent of patients ($n = 6$) presented with vertigo. In contrast, additional abnormalities of balance, such as instability and axial deviation, were detected in 45% of patients ($n = 9$).

The average EDSS score was 1.3. In addition, six (30%) individuals were asymptomatic. The MRI of brain revealed infratentorial lesions in 55% of patients. In 37% of cases, these lesions affected the brainstem; in 27% of cases, they affected the cerebellum; and in 36% of cases, they affected both regions (Fig. 2).

In our study, eye movement anomalies were prevalent. In fact, abnormal saccadic latencies are reported in 80% of cases (16 patients), and low saccade velocity is observed in 40% (8 patients). This decrease in speed reveals subclinical ocular motor paresis. In 50% of cases ($n = 10$), precision anomalies such as dysmetria are seen: 35% of instances have hypermetric saccades, and 15% have hypometric saccades. Dysmetria is often linked to cerebellar involvement (Fig. 3).

Concerning the tracking test, 60% of our MS patients ($n = 12$) exhibited saccadic phenomena, which was a result of low gain in pursuit eye movements (Fig. 4).

Considering ocular motor symptoms of vestibulo-ocular pathways involvement, we discovered a case of pendular nystagmus and another case of positional nystagmus. Secondary progressive multiple sclerosis (SPMS)

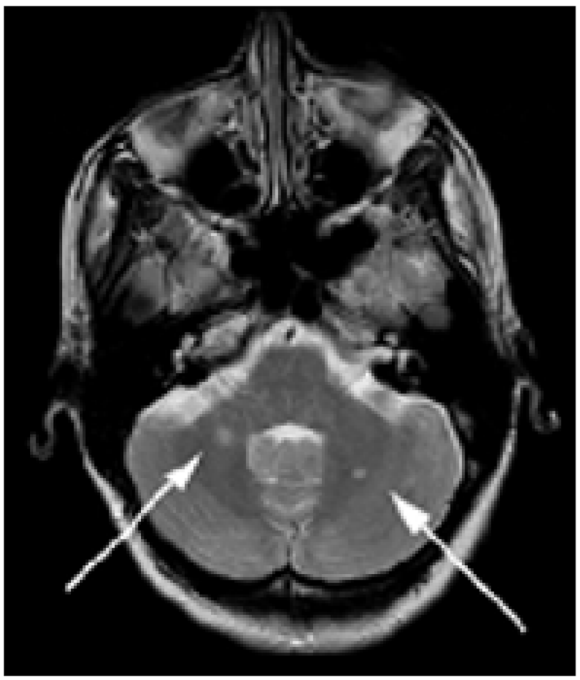

Fig. 2 Brain MRI showing two MS lesions (white arrows) in the cerebellar white matter

manifested as pendular nystagmus in a 56-year-old female patient. In addition to instability, this patient also exhibits left hemiparesis, left hemiparesis, oculomotor paralysis, and central vestibular syndrome.

A 26-year-old male with RRMS presented with central positional nystagmus manifesting as a torsional nystagmus beating toward the ground induced by left side Dix-Hallpike test, with central signs as the nystagmus was triggered without latency, non-fatigable, lasting more than 30 s, and uninhibited by ocular fixation. The MRI of this patient revealed brainstem lesions.

No patient exhibited a gaze-evoked nystagmus. In 55% of instances (11 patients), low gain with reduced slow-phase velocity was seen. In those cases, 8 patients had brainstem and/ or cerebellar lesions.

The caloric test investigates the horizontal vestibulo-ocular reflex (H-VOR) at extremely low frequencies using water or air stimulation at 44 °C and 30 °C which is 7 °C above and below body temperature, respectively. Labyrinthine paresis and directional preponderance are the most common caloric anomalies in our series. Labyrinthine paresis was identified in 50% of patients (left LP in 15% of cases and right LP in 35% of cases), and directional preponderance was reported in 50% of cases (25% left and 25% right).

Table 2 summarizes demographics, clinical, VNG, and imaging data of our series

Discussion

Eye movement disorders in MS are frequently misdiagnosed and frequently overlooked during clinical examination. Even at a subclinical state, these defects frequently cause disability and weariness [11].

Regarding eye movements impairment, abnormal saccades are very prevalent in MS, occurring in 30% Cipparrone et al. [12] patients, 36% of Degirmenci et al. [8] cases, and 65% of Kenig et al. [13] cases. Recording saccades permits the evaluation of subclinical ocular motor disorders. Using ENG, Grénman examined the three characteristics of saccadic movements (precision, velocity, and latency). In 36% of cases, prolonged latencies were observed [14]. However, this characteristic is affected by various variables, including age, brightness, simultaneous auditory stimulus, and visual acuity. Brainstem lesions are strongly associated with low saccade velocity. In fact, saccade velocity slowed to as low as 200°/s often. Dysmetria is associated with cerebellar lesions [15]. It was identified in 44% of patients in the Grenman series [16], 32% of cases in the Serra et al. [17] series, and 45% in our study.

Smooth pursuit anomalies are widespread (30 to 70%) in MS [8, 12, 14, 15, 18, 19]. An isolated gain deficiency in pursuit eye movements is uncommon, and it is frequently accompanied with abnormalities in saccades, particularly dysmetria [16]. In MS, abnormal OKN is commonly observed. Both brainstem and cerebellar lesions have been associated with a decreased velocity of the OKN slow phase. Eleven individuals in our series revealed abnormal OKN. The MRI of their brains indicated infratentorial lesions in 82% of instances. In addition, it was revealed that individuals with brainstem lesions had slower saccade velocities than those with cerebellar involvement [14, 20]. However, Cogan et al. [21] mention pathologic OKN as one of the ocular symptoms indicating cerebellar involvement. On the contrary, precision problems are more closely associated with cerebellar disorders [22].

Different lesions of the central nervous system, particularly infratentorial placement, are associated with tracking problems [23, 24]. More than half of the eleven patients with infratentorial lesions in our research showed abnormal tracking results.

MS patients may have peripheral or central vestibular abnormalities. Overall prevalence of real vertigo is less than 5% [25]. However, complaints regarding imbalance and other balance disorders are more frequent.

In MS, nystagmus is more prevalent during relapses. In his sample of 56 MS patients with balance difficulties during relapses, Cohen [26] reported nystagmus in 64% of cases; nearly half of them had central type nystagmus. In MS, acquired pendular nystagmus is present

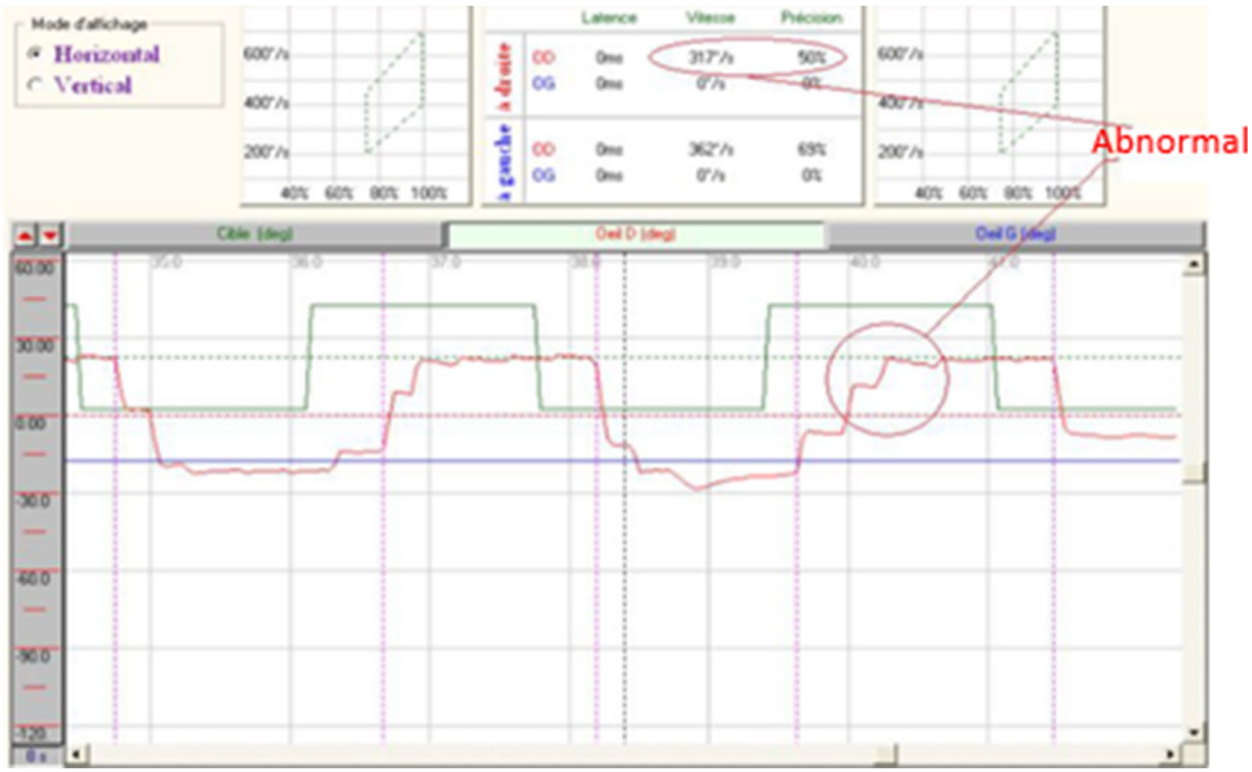

Fig. 3 Pathologic saccades with low velocity and hypometria (green graph, target movement; red graph, eye saccadic movement)

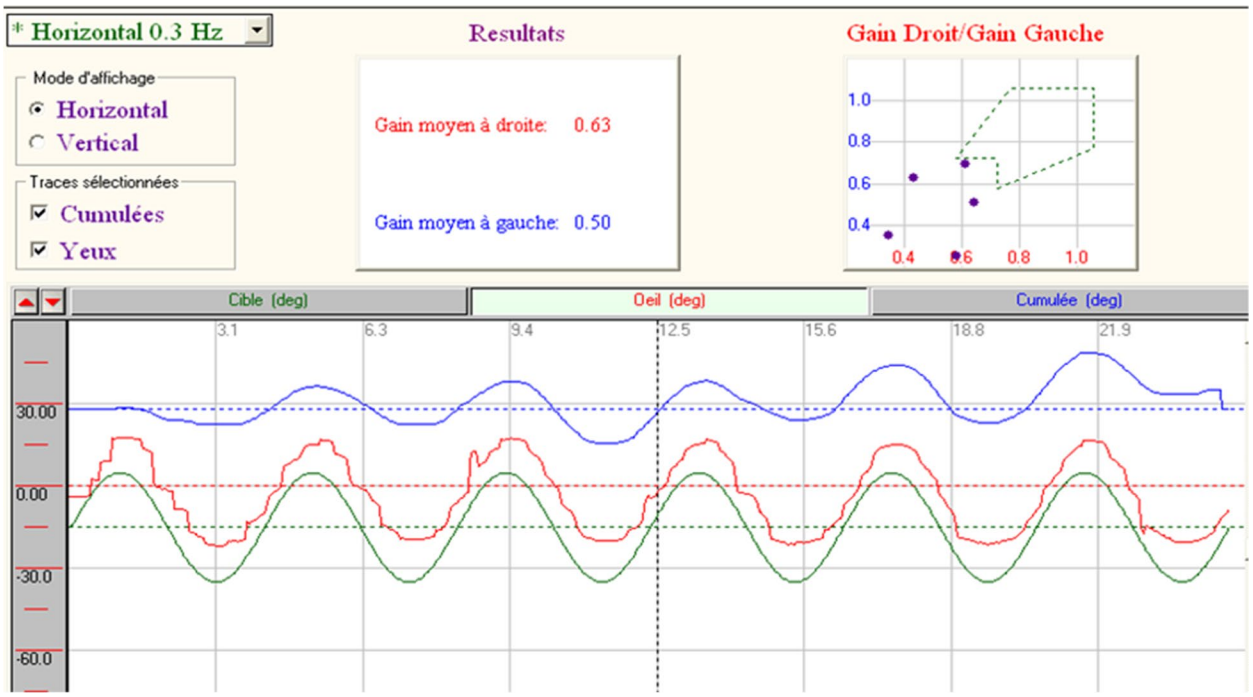

Fig. 4 Pathologic tracking test with low gain of pursuit movements and saccadic events (green graph, target movement; red graph, eye saccadic movement)

Table 2 Demographics, clinical, VNG, and imaging data of our series

Patient	Age	Gender	MS type	EDSS	Balance disorder/ rotatory vertigo	Videonystagmography							MRI
						Spontaneous nystagmus	Saccades			OKN (gain)	Gaze nystagmus	Caloric testing	
							Accuracy	Latency	Maximum velocity				
1	26	F	RRMS	0	BD	-	Normal	Abnormal	Low	Normal	-	RHV	No posterior fossa lesion
2	59	M	RRMS	1	BD	-	Normal	Normal	Normal	Low[a]	-	RHV	Cerebellum
3	56	F	SPMS	4	BD	Pendular	Hypermetric	Normal	Normal	Normal	-	RP	No posterior fossa lesion
4	47	F	RRMS	2	BD	-	Normal	Normal	Normal	Low[a]	-	Normal	Brainstem
5	31	F	RRMS	1	RV	-	Hypermetric	Abnormal	Normal	Normal	-	RHV	No posterior fossa lesion
6	29	M	RRMS	2.5	RV	-	Normal	Abnormal	Normal	Low[a]	-	RP	Brainstem & cerebellum
7	44	F	RRMS	2	-	-	Normal	Abnormal	Normal	Low[a]	-	RHV+ Left P	No posterior fossa lesion
8	27	F	RRMS	0	RV	-	Normal	Abnormal	Normal	Low[a]	-	Normal	Brainstem & cerebellum
9	44	M	RRMS	0	-	-	Normal	Abnormal	Normal	Low[a]	-	LP+ LHV	No posterior fossa lesion
10	55	F	RRMS	1	-	-	Hypermetric	Abnormal	Normal	Normal	-	LP+LHV+ left P	No posterior fossa lesion
11	54	F	RRMS	2.5	-	-	Normal	Abnormal	Low	Normal	-	LP+LHV+ RP	No posterior fossa lesion
12	26	M	RRMS	4	RV	Positional	Hypermetric	Abnormal	Normal	Normal	-	Normal	Brainstem & cerebellum
13	49	F	RRMS	2	BD	-	Normal	Abnormal	Low	Low[a]	-	Left P	Brainstem
14	26	F	RRMS	1	BD	-	Hypometric	Abnormal	Low	Low[a]	-	LP	Cerebellum
15	53	F	RRMS	2	RV	-	Hypermetric	Abnormal	Normal	Normal	-	RP	Brainstem
16	39	F	RRMS	1	BD	-	Hypermetric	Abnormal	Low	Normal	-	LHV	Brainstem & cerebellum
17	30	F	RRMS	0	-	-	Normal	Abnormal	Normal	Low[a]	-	Normal	Cerebellum
18	33	F	RRMS	1	BD	-	Hypermetric	Abnormal	Low	Normal	-	LP+ RHV	No posterior fossa lesion
19	24	M	RRMS	0	RV	-	Normal	Normal	Low	Low[a]	-	RHV+ Left P	No posterior fossa lesion
20	30	F	RRMS	0	BD	-	Hypometric	Abnormal	Low	Low[a]	-	RP	Brainstem

F Female, *M* Male, *RRMS* Relapsing-remitting type of multiple sclerosis, *SPMS* Secondary progressive multiple sclerosis, *RV* Rotatory vertigo, *BD* Balance disorder, *RHV* Right hypovalence, *RP* Right preponderance, *LHV* Left hypovalence, *LP* Labyrinthine paresis, *Left P* Left preponderance. [a]Reduced slow-phase velocity

in 11 to 20% of the cases, often accompanied by internuclear ophthalmoplegia or optic neuropathy, and most frequently observed in the progressive form of the disease [13, 17, 27]. A total of 6.7% of MS patients present with central positional type nystagmus [28].

In MS, caloric testing reveals anomalies in H-VOR, vestibular reflectivity, and directional predominance. H-VOR abnormalities are really one of the most prevalent ocular motor abnormalities in MS. In 36% of MS sufferers, Downey et al. [29] identified VOR abnormalities. In half of the patients in our series, VOR gain abnormalities were found (10 patients). Seven patients (35%) had hyporeflectivity (VOR low gain), while three patients (15%) exhibited hyperreflectivity. A reduction in VOR gain is often associated with bilateral peripheral vestibular lesions or lesions of the brainstem [30]. In contrast, an unusually elevated VOR gain is uncommon and is typically linked with cerebellar lesions [31]. Caloric directional preponderance was seen in 28% of Aantaa et al [32].'s series, 48% of Grenman's [33] series, and 50% of our series.

The underlying pathophysiology is related to the mechanism of stable gaze holding that requires a neural integrator that converts the pulses of neural firing into a constant firing rate.

The integrator relies on feedback, altered feedback behaves as an "unstable" integration if it is too strong, and as a "leaky" integration if it is too weak [34].

Horizontal eye movement neural integrator is located in the pons (paramedian pontine reticular formation) and upper part of the medulla (nucleus prepositus hypoglossi and medial vestibular nucleus). Feedback information is delivered from the cerebellum (fastigial nucleus, dorsal vermis, flocculus, and nodulus).

The medial vestibular nucleus is a key element for neural integration of horizontal eye movements. It receives feedback from various cerebellum and brainstem structures such as flocculus and nodulus [34]. Cerebellar feedback deficit manifests as neural integrator decreased gain and reveals its inherently imperfect behavior, resulting in a decelerating drift in eye position followed by a visually driven corrective saccade (quick phase of the jerk nystagmus) that refocuses the eye on the area of interest on target. Drift velocity increases as the eye moves away from the center [34–37].

In rare cases, the slow-phase velocity of the drift increases exponentially; this phenomenon, known as increased frequency or "runaway" nystagmus, can also be explained by an increase in feedback gain, resulting in instability of the neural integrator [34, 35].

Other factors can also explain jerky oscillations in subjects with multiple sclerosis such as vestibular alteration or hypofunction due to the demyelinating plaque affecting the vestibular nuclei which manifest as peripheral vestibular lesion [34].

Conclusion

For MS patients with an average EDSS score of 1.3, it is believed that vestibular symptoms, particularly ocular motor abnormalities, are highly prevalent in the first stages of the illness. These abnormalities are often not taken into account in disability rating scales such as EDSS. Systematic assessment of nystagmus, saccades, and VOR examination in MS patients, whether they were symptomatic or not, could help diagnose more brainstem and cerebellum dysfunctions. Our study using monocular assessment VNG disclosed several ocular motor abnormalities is apparently asymptomatic patients. However, future extension of the study with binocular VNG system could answer questions related to the extent to which abnormalities of conjugate eye movements exist in MS patients.

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Authors' contributions
NO was involved in establishing the study protocol and manuscript drafting, SAGh was involved in literature review, collecting data and drafting of the manuscript, SB and MFB were involved in collecting data and reviewed the manuscript, MR was involved in establishing the study protocol and reviewed the manuscript, MNA reviewed the manuscript for insightful remarks. All authors read and approved the final manuscript.

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Availability of data and materials
The datasets generated and/or analyzed during the current study are not publicly available due to patients' data confidentiality but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The IRB approved our study, and consents to participate to the study were signed by the patients. Our IRB is CEHUF (comité d'ethique hospital-universitaire de Fès), and email is Comite.ethique.fes@usmba.ac.ma.

Consent for publication
An informed consent for publication purpose was obtain from the patients. Written consent is available.

Competing interests
The authors declare that they have no competing interests.

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