Ocular Torsions and the Subjective Visual Vertical with Brainstem and Cerebellar Lesions in Multiple Sclerosis.

Original Article

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ABSTRACT

Background: Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system that makes a burden on patients and their families leading to disability especially in young patients. Acute or chronic lesions of MS within the brainstem and cerebellum frequently results in ocular motor disorders and deviation of subjective visual vertical (SVV).
Aim: Finding a feasible, convenient way to evaluate ocular motor disorders in MS patients with brainstem and cerebellar affection and also to investigate to what extent they have problems with the estimation of verticality and also to demonstrate the relationship with stages of MS and expanded disability status scale (EDSS).
Patients and Methods: Here, an observational case control study involving 95 patients: 65 patients with relapsing remitting multiple sclerosis all with brainstem and/or cerebellar affection and 30 healthy age and gender matched individual. MS patients were subjected to complete bedside evaluation, oculomotor testing and SVV testing while control group were subjected to subjective visual vertical evaluation.
Results: The study found that MS patients with brainstem and/or cerebellar affection experienced variety of ocular motor disorders. SVV abnormalities were detected with both cerebellar and brainstem lesions. SVV showed a highly statistically significant difference in both groups.
Conclusion: Clinical examination of eye movement and also SVV evaluation, takes only a few minutes to perform, but provide better information concerning the presence of brainstem and cerebellar involvement in MS patients.

Key Words: Brainstem, cerebellum, multiple sclerosis, oculomotor disorders, subjective visual vertical.

Received: 30 April 2021, **Accepted:** 30 July 2021

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ISSN: 2090-0740, 2024

INTRODUCTION

Multiple Sclerosis (MS) is a neurodegenerative disease with inflammatory-mediated demyelination of axons throughout the central nervous system[1]. The disease contributes to cognitive, motor, and sensory dysfunction that sometimes undistinguished from other causes through the disease lifespan[2]. Being more prominent in females and in younger adults[3], MS neurological disorders affect patients' quality of life through a number of neurological deficits such as vertigo, sensory loss, impaired vision, binary vision, and ataxia[4] through disease patient's lifespan. Although its cause is still vague, genetic, environmental, immunological factors could raise the disease[5]. Patients swing between relapsing-remission phases till years later they present with progressive phase of the disease[6].

Brainstem is commonly affected in MS presented by double vision, internuclear ophthalmoplegia (INO) and vertigo (due to cranial nerves affection), less commonly presented by hearing loss and severe bulbar signs. Cerebellar involvement cause unilateral ataxia, dysmetria or dysdiadokinesia[7]. Disruption of the cerebellopontine networks can cause also acquired pendular nystagmus[8].

Ocular motor disorders such as INO, disturbances of conjugate gaze, such as saccadic dysmetria and impaired smooth pursuit, gaze-evoked nystagmus, and vestibulo-ocular reflex abnormalities often occur as early manifestations or during the course of the disease[9], so they are a useful diagnostic signs about brainstem and cerebellar function by focusing on dynamic aspects of eye movement[10]. Clinical tests that are most sensitive to those dynamic aspects are saccades (the rapid eye movements by which we shift our point of regard from one object to another) and the vestibulo-ocular reflex which holds gaze on target during head perturbations[11].

Subjective visual vertical (SVV), which is the measurement of the patient's ability to judge when a slit

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of light is earth vertical in a dark room is a promising test in MS patients[11]. SVV has been measured in variable clinical situations as peripheral and central vestibular lesions[12], disorders of central vestibular-ocular system[13] and multiple sclerosis[14]. *Brandt and Dieterich*[15] proposed that SVV is an otolith function test and a sensitive sign of brainstem dysfunction.

In the current study, we employed: bedside testing (including head impulse and skew deviation), oculomotor testing (testing for saccades, smooth pursuit, optokinetic) and subjective visual vertical testing to provide a profile of those simple tests that is well tolerated by the patients in brainstem and cerebellar involvement in MS, so could be considered as a complementary oto-neurological tool for evaluation of MS patients; and also to investigate to what extent patients with MS, may have problems with the estimation of verticality.

PATIENTS AND METHODS:

Subjects:

The study was designed as an observational case control study. The study was approved by the Research Ethical Committee and Otolaryngology department of Faculty of Medicine, Cairo University. An informed consent was signed by all subjects for participation in the study. Ninety-five subjects were included in the study, 65 patients as a study group and 30 subjects as a control group.

Study group:

All patients in the study group fulfilled the following inclusion criteria: 1) All patients with relapsing remittent type of MS. 2) Patients having cerebellar or⁄and brain stem affection. 3) Duration of illness from one to five years. 4) EDSS from 2 to 5[16]. 5) Age from 18 to 50 years old. 6) Both genders are encountered.

Exclusion Criteria: Patients at the time of examination with the following were excluded: 1) Patients with: Oculomotor paresis, Inter-nuclear ophthalmoparesis and severe visual disturbances. 2) Patients suffering from other co morbid diseases (diabetes, hypertension). 3) Patients suffering from inner ear diseases. 4) Non-ambulatory patients.

They were selected from MS unit, Neurology Department of Kasr Al-Ainy Hospital, Cairo University, evaluated in Audiology Clinic, ENT department of Kasr Al-Ainy Hospital for vestibular assessment during the pe¬riod from March 2016 till October 2017.

Control group

Healthy individuals with age and gender matching the study group. They were collected from relatives of patients attending audiology clinic, ENT department of Kasr Al-Ainy Hospital with no history of neurological problem or demyelinating disease.

Methodology

The study group subjected to:

- Full history taking according to the standard Neurology sheet of Kasr Al-Ainy MS unit, Neurology department.

- Full Neurological examination.

- Opthalmologic examination (visual acuity, ocular motility)

- Radiological assessment by MRI (Magnetic Resonance Imaging) with and without contrast. Axial T1, T2 & FLAIR. It was done at Radiology department Kasr Al-Ainy hospital and assessed by an experienced radiologist for:

- Diagnosis of MS done according to Revised Mcdonald's criteria[17] and Barkhof criteria for dissemination in space[18, 19].

- The number of Black holes which is defined as any hypotense region visible on T1-weighted images coincident with a region of high signal intensity on T2-weighted images[20]. The black holes have been shown to be areas of axonal loss on histopathology[21].

- Assessment of disease severity by Expanded Disability Status Scale (EDSS)[16].

- Vestibular bedside evaluation:

1- Skew Deviation: we assessed skew deviation using the cover test. This involved covering one eye and detecting a corrective vertical movement of the other eye.

2- Spontaneous nystagmus: observation of the direction and the effect of gaze on the intensity and direction of the nystagmus were done, also removal of visual fixation using Frenzel glasses that have 20-diopter convex lenses to prevent fixation and to magnify eye motion.

3- Gaze-evoked nystagmus: we asked patients to fix their gaze on a target, 30° to the right, 30° to the left and in the center position. Pathological nystagmus was regarded as any sustained nystagmus which occurred under these conditions.

4- Head-shaking nystagmus: the patient's head was shaken horizontally in a sinusoidal fashion at a rate of about 2-3 Hz with amplitude of 20° for 15 seconds after pitching the head forward by approximately 20° to bring the horizontal semicircular canals (HCs) into the plane of stimulation, Evaluation of head-shaking nystagmus was done according to *Huh and Kim*[22].

5- Head impulse test: we asked the patient to fixate upon a target in front of the eyes and then briskly turned the patient's head horizontally with low amplitude (10-20°) and a high acceleration (2000-4000°/second).

6- Dix Hallpike Positioning test: The patient's head was turned 45 degrees to one side and the patient was laid supine with his head over the end of the examination bed. The patient's eyes were observed for nystagmus, and the patient was asked if he felt dizzy. This position was held for at least 30 seconds, the result was positive if the patient developed symptoms (vertigo) and nystagmus then the test was repeated on the opposite side.

7- Positional Tests: we included the following positions: Sitting, supine, head right, head left, body right and body left. The patient was asked to lie still in each position for 30 seconds and observation for nystagmus was done.

• *Oculomotor testing:*

1- Saccadic tracking; Random horizontal saccades (measuring Latency, Speed, Accuracy) was elicited by visual dots presented at random frequency, alternating between 15° and 30° horizontal positions to right or left.

2- Optokinetic tracking; at 30°/s (measuring gain; ratio of field velocity to eye velocity). Moving dots directed by light bar were used at the designated speed.

3- Smooth pursuit; was elicited by a dot moving sinusoidally in the horizontal plane (amplitude: 30°) to right and left at 0.1 Hz, 0.2 Hz, 0.4 Hz (measuring gain & inaccuracy being determined by the presence of corrective saccades).

• *Subjective visual vertical test (both for the study group and the control group):*

We performed the test in a totally dark room to prevent visible landmarks. Subjects were sitting in front of a screen where a straight laser line was projected. The line was presented 10 times in one condition: both eyes viewing (five times in both directions, in random order) and the average were calculated. Subjects were asked to adjust the line to the gravitational vertical with a hand-held infrared remote-controlled potentiometer.

Before measuring, the system was adjusted to vertical with the aid of a plumb line and we assured that vision and visual field of the participants were sufficient to perform the test. During the measurements, the subjects sat with their heads in an erect position with spectacle correction if necessary. Time and corrections were not limited. No information was given on the performance. After finishing, the lights were turned on and the subjects head position was checked.

Performance in the SVV adjustments expressed as the deviation from gravitational vertical (0º) measured in degrees with a precision of 0.1º. In an upright static position, normal individuals align the linear marker within ~ ± 2 degrees of true (gravitational) vertical (0 degrees). Positive values indicate deviations of the upper pole of the light bar to the right (as seen by the individual), and negative values indicate deviations of the upper pole of the light bar to the left[23].

Equipment:

1) MRI (Magnetic Resonance Imaging): 1.5 tesla unit Intera Philips medical systems. Axial T1, T2 & FLAIR.

2) Subjective visual vertical test: we used DIFRA Instrumentation VISIOSTAR II with Disoft software version 1.30.04, NYSSTAR I camera. Windows 7 Ultimate, Processor Intel® Core™ i3-2120 CPU @ 3.30GHz, RAM 4GB, 32-bit Operating system.

3) Oculomotor testing: Using Micromedical computerized 2-channel VNG with monocular goggles, micromedical Technologies Inc., Spectrum software, Chatham, Illinois, USA.

Statistical Methods:

The clinical data were recorded on a report form. These data were tabulated and analyzed using the computer program SPSS (Statistical package for social science) version 20 to obtain:

Descriptive data:

Descriptive statistics were calculated for the data in the form of:

1. Mean, median and standard deviation for quantitative data.
2. Frequency and distribution for qualitative data.

Analytical statistics:

In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests:-

1. Student's t-test and Mann-Whitney test (Z test): - Used to compare mean of two groups of quantitative data of parametric and non-parametric respectively.

2. ANOVA test (F value) and kruskal-wallis test: - Used to compare mean of more than two groups of quantitative data of parametric and non-parametric respectively.

3. Inter-group comparison of categorical data was performed by using chi square test (X^2-*value*) and fisher exact test (FET).

$$x^2 = \frac{\sum (observed - \exp ected)^2}{Expected}$$

$$Expected = \frac{col\ .total \quad x\ row \quad total}{Grand \quad total}$$

4. Correlation coefficient: - to find relationships between variables.

A *P value <0.05* was considered statistically significant (*) while *>0.05* statistically insignificant *P value <0.01* was considered highly significant (**) in all analyses.

RESULTS:

The current study included 95 subjects divided into two groups:

The study group included 65 patients with age ranging from 18 to 50 years with a mean age of 31.12 ± 8.17 years. They were 23 males and 42 females. All the patients included in the study group have relapsing-remitting multiple sclerosis where 52 patients were in remission and 13 patients were in relapse. The duration of the disease was ranging from 1 to 5 years with a mean of 3.08 ± 1.65 years. The EDSS included was from 1 to 5 with a mean of 3.37 ± 1.11. **Control group** included 30 healthy age & gender matched individuals with age ranging from 18 to 49 years with a mean age of 30.87±8.33 years. They were 12 males and 18 females. No statistically significant difference was detected between the 2 groups regarding age and gender.

Bedside evaluation:

Eight patients of the study group had spontaneous nystagmus which was not suppressed by visual fixation. Fourteen patients had gaze evoked nystagmus, most of them with horizontal direction, 8/14 had spontaneous nystagmus. Eighteen patients with positive post head shake test, 13 with horizontal nystagmus, 3 with vertical nystagmus and 2 with torsional nystagmus. Fifty patients with nystagmus in dix-hallpike, nystagmus had no delay, no habituation and no reversal while sitting from supine position. Forty-six patients with nystagmus on positional testing, results presented in (Table 1).

Table 1: Bedside tests evaluation:

Bedside test	Positive		Negative	
	NO	%	NO	%
Spontaneous nystagmus	8	12.3	57	87.7
Gaze evoked nystagmus	14	21.5	51	78.5
Post head shake	18	27.7	47	72.3
Dix HallPike	50	76.9	15	23.1
Positional	46	70.8	19	29.2

Thirty- six patients with positive head impulse test (correction saccade). Fifteen patients with positive skew deviation (8 patients with cerebellar affection, 2 patients with brainstem affection and 5 patients with combined cerebellar and brainstem affection). Normal head thrust and abnormal skew deviation in 4 patients. Abnormal head thrust and abnormal skew deviation in 11 patients (Table 2).

Table 2: Head impulse and skew deviation in study group:

	Head impulse		Skew deviation	
	No.	%	No.	%
Positive	36	55.4	15	23.1
Negative	29	44.6	50	76.9
Total	65	100	65	100

Oculomotor testing:

Saccades: Twenty-one patients of the study group had slow velocity, seven patients with abnormal accuracy and twenty-five patients of the study group had delayed latencies as in (Table 3).

Table 3: saccade in study group:

Saccade	No.	%
Velocity saccade		
Normal	16	24.6
Borderline	28	43.1
Slow	21	32.3
Accuracy saccade		
Undershot	6	9.23
Normal	58	89.23
Overshot	1	1.54
Latency saccade		
Normal	40	61.5
Delayed	25	38.5

Smooth pursuit: Thirty-two patients (49.2%) of the study group had low pursuit gain while Forty-two patients of the study group (64.6%) had correction saccade.

Optokinetic: Fifty patients (76.9%) of the study group had low 30º gain, also optokinetic was asymmetrical in 8 patients (12.3%).

Subjective visual vertical:

Ten patients of the study group have abnormal subjective visual vertical, three with brainstem affection, three with cerebellar affection and four with both brainstem and cerebellar affection. Three of the ten patients with abnormal SVV were in relapse while seven were in remission.

In table 4, comparison between study and control groups regarding deviation of SVV shows a highly statistically significant difference between the groups in right, left and average SVV. Comparison between different stages of MS namely; remission and relapsing phases as shown in table 5 shows no statistically significant difference. Table 6 shows SVV abnormalities with combined cerebellar and brainstem lesions where a statistically significant difference was found between right SVV abnormalities with both cerebellar and brainstem lesions (*P= 0.03*). Table 7 shows a statistically significant difference between right SVV abnormalities with cerebellar and/or brainstem lesions (*P=0.04*).

Table 4: Comparing subjective visual vertical in study and control groups:

Subjective visual vertical	Case group (65)			Control group (30)			Z(man Whitney test)	*P value*
	Mean	SD	Median	Mean	SD	Median		
Right (CW)	0.86	0.76	0.6	0.47	0.36	0.4	2.7	0.0007**
Left (CCW)	0.93	0.84	0.7	0.39	0.38	0.3	3.5	<0.001**
Average SVV	0.89	0.74	0.7	0.43	0.29	0.33	3.46	0.001**

CW: clockwise; CCW: anticlockwise
P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Table 5: Comparing subjective visual vertical in different MS stages:

Stages of MS		Remission (52)			Relapse (13)			Z(man Whitney test)	*P value*
		Mean	SD	Median	Mean	SD	Median		
Subjective visual vertical	Rt (CW)	0.86	0.80	0.6	0.84	0.62	0.9	0.25	0.8
	Lt (CCW)	0.90	0.83	0.7	1	0.93	0.9	0.49	0.62
	average	0.81	0.31	0.67	1.2	1	0.8	1.3	0.17

CW: clockwise; CCW: anticlockwise
P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Table 6: Subjective visual vertical association with cerebellar & brainstem lesions:

		Cerebellar & brainstem (31)			Single lesion (34)			Z test	*P value*
		Mean	SD	Median	Mean	SD	Median		
Subjective visual vertical	Rt	0.67	0.62	0.5	1	0.84	0.8	2.2	0.03
	Lt	0.8	0.75	0.5	1	0.91	0.9	1.1	0.3*
	average	0.92	0.66	0.8	0.86	0.81	0.62	0.84	0.39

P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Table 7: Subjective visual vertical abnormalities association with cerebellar and/or brainstem lesions:

		Cerebellar & brainstem (31)			Cerebellar (23)			Brainstem (11)			Kruskal-wallis test	*P value*
		Mean	SD	Median	Mean	SD	Median	Mean	SD	Median		
SVV	Rt	0.67	0.62	0.5	0.98	0.94	0.7	1	0.63	1.1	6.6	0.04*
	Lt	0.8	0.75	0.5	0.98	0.96	0.9	1.2	0.84	0.9	2.1	0.3
	Average	0.92	0.66	0.8	0.86	0.88	0.60	0.85	0.69	0.75	0.89	0.64

SVV: subjective visual vertical; Rt: right; Lt: left.
P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Regarding head impulse or skew deviation abnormalities associated with SVV, tables 8 and 9 shows no statistically significant difference. Also, head impulse or skew deviation abnormalities in patients with different MS stages show no significant difference as shown in (Tables 10 & 11). As well, no statistically significant difference was found between skew deviation or head impulse abnormalities with cerebellar, brainstem, or both cerebellar and brainstem affections (Tables 12 & 13). Finally, Pearson's correlation coefficient was done in regards to SVV association with EDSS or disease duration where table 14 shows significant correlation between disease duration and left SVV (*P=0.04*) and table 15 shows no significant association between SVV and the EDSS.

Table 8: Head impulse abnormalities with subjective visual vertical:

Head impulse	Rt SVV					Lt SVV					Total SVV				
	Mean	SD	Median	Z test	*P value*	Mean	SD	Median	Z test	*P value*	Mean	SD	Median	Z test	*P value*
Positive	0.93	0.89	0.60	0.84	0.63	1	0.95	0.90	0.33	0.74	0.99	0.83	0.80	1.1	0.25
Negative	0.79	0.64	0.65			0.88	0.79	0.65			0.82	0.67	0.65		

SVV: subjective visual vertical
P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Table 9: Skew deviation abnormalities with subjective visual vertical:

Head impulse	Rt SVV					Lt SVV					Total SVV				
	Mean	SD	Median	Z test	*P value*	Mean	SD	Median	Z test	*P value*	Mean	SD	Median	Z test	*P value*
Positive	0.79	0.71	0.60	1.1	0.3	0.87	0.75	0.90	0.51	0.6	0.84	0.68	0.70	0.81	0.41
Negative	1	0.9	0.90			1.1	1	1.1			1	0.93	0.80		

SVV: subjective visual verticals
P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Table 10: Head impulse abnormalities in patients with different MS stages.

Stages of MS		Remission (52)		Relapse (13)		X^2	*P value*
		No	%	No	%		
Head impulse	Positive	29	55.8%	7	53.8%	0.016	0.90
	Negative	23	44.2%	6	46.2%		

P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Table 11: Skew deviation abnormalities in patients with different MS stages.

Stages of MS		Remission (52)		Relapse (13)		FET	*P value*
		No	%	No	%		
Skew deviation	Positive	12	23.1%	3	23.1%	0.0	1.0
	Negative	40	76.9%	10	76.9%		

P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Table 12: Head impulse abnormalities with cerebellar and/or brainstem lesions:

Head impulse	Cerebellar & brainstem (31)		Cerebellar (23)		Brainstem (11)		FET	*P value*
	No	%	No	%	No	%		
Positive	18	58.1%	13	56.5%	5	45.5%	0.60	0.76
Negative	13	41.9%	10	43.5%	6	54.5%		

P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Table 13: Skew deviation abnormalities with cerebellar and/or brainstem lesions

Skew deviation	Cerebellar & brainstem (31)		Cerebellar (23)		Brainstem (11)		FET	*P value*
	No	%	No	%	No	%		
Positive	5	16.1%	8	34.8%	2	18.2%	2.61	0.28
Negative	26	83.9%	15	65.2%	9	81.8%		

P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Table 14: Correlation between duration of the disease and SVV in study group

Subjective visual vertical	Duration of disease	
	rho	*P value*
Right (CW)	0.04	0.78
Left (CCW)	0.3	0.04*
Average SVV	0.04	0.74

CW: clockwise; CCW: anticlockwise
P value is considered significant if *P <0.05*, highly significant if *P <0.001*

Table 15: Correlation between EDSS and SVV in study group

Subjective visual vertical	Duration of disease	
	rho	*P value*
Right	-0.03	0.85
Left	-0.11	0.51
Average SVV	0.3	0.06

EDSS: Expanded Disability Status Scale
P value is considered significant if *P <0.05*, highly significant if *P <0.001*

DISCUSSION

In the present study, bedside evaluation revealed 8/65 patients with spontaneous nystagmus (12.3%) which is consistent with *Farid et al*[24]. who reported spontaneous nystagmus in 2/50 of MS patients (4%) with a down beating axis of rotation yet our study had much higher percentage. Also, *Serra et al*.[11] and *Derwenskus and colleagues*[25] have found pendular nystagmus in central position in 2/50 of MS patients (4%). As well, *Downey et al*.[10] reported 4/50 of patients (8%) with nystagmus in central position (3 with pendular and one with down beating nystagmus) revealing an association of central affection in MS. Earlier investigators as *Mangabeira-Albernaz et al*.[26] assumed spontaneous nystagmus is a frequent sign of MS with vertical, diagonal, rotatory and dissociated being the most frequent types. These findings were supported by *Cipparrone et al*.[27].

For gaze evoked nystagmus (GEN), 14/65 patients (21.5%) of the study group showed GEN. Gaze evoked is a common finding in MS as it indicates neural integrator affection with high number of brain stem lesions[28], which included in our study. Many studies had similar findings as ours namely; *Servillo et al*.[29] with 22/163 of MS patients (13.5%) had GEN, *Negm et al*.[30] with 7/54 patients (12.96%) also with GEN. *Downey et al*.[10] and *Derwenskus et al*.[25] reported similar results with 8/50 MS patients with GEN. *Tilikete et al*.[9] found that almost half of the patients with gaze evoked were in the relapsing-remitting form of MS which is matching to our cases and not associated with INO with is the same as our exclusion criteria.

Post head shaking nystagmus was positive in 18/65 patients of our study group (27.7%). This is consistent with *Farid et al*.[24] who reported 13/50 MS patients (26%) with positive post headshake, 11 with horizontal nystagmus, and 2 with vertical nystagmus. The cross coupled response (downbeat nystagmus after horizontal head shaking) that occurred in 15% was owed to cerebellar dysfunction[31].

In our study 36/65 patients (55.4%) of the study group had positive head thrust test at the bedside vestibular evaluation reflecting the dynamic imbalance of the vestibular system. In other studies as *Farid et al*.,[24] the head thrust test was positive in 20/50 MS patients, *Servillo et al*.[29] reported 16/163 patients (9.8%) (150 patients with definite multiple sclerosis and 13 patients with clinically isolated syndrome) with pathological VOR, *Serra et al*.[11] reported also impaired VOR in 11/50 patients, *Derwenskus et al*.[25] and *Downey et al*.[10] showed similar results with 8/50

MS patients with impaired VOR. The head thrust is a sensitive clinical test of the dynamic aspects of eye movement beside saccadic testing[11]. Focusing on dynamic eye movement gives more information about brainstem and cerebellar function[10]. This explains the raised percentage in our sample, as we included cases with brainstem and cerebellar affection unlike other studies.

Using cover test to test for correct ocular alignment, skew deviation was found in 15 patients (23.1%) of the study group. Skew deviation with higher eye is most commonly in midpoint and midbrain lesions while lower one points to medullary lesions. In addition to change in alignment, the higher eye is usually intorted while the lower eye extorted. Taken together, these features when combined with deviation of the subjective visual vertical are referred to as the ocular tilt reaction[28]. Our findings and conclusion match other findings by *Downey et al*.[10], *Serra et al*.[11], *Servillo et al*.[29].

No significant results were detected between head impulse or skew deviation abnormalities in MS patients with brainstem, cerebellar, or both as well, also regarding abnormalities in stages of MS. Limited data were available to compare with our findings.

In the present study, saccadic testing revealed that the most common abnormality was delayed latencies in 25 patients (38.5%) followed by slow velocity in 21 patients (32.3%) then saccadic dysmetria in 7 patients (10.8%) taking the form of either overshoot in only one patient presenting 1.54% of the cases or undershoot in 6 patients (9.23%). In line with our study, *Servillo et al*.[29] reported saccadic dysmetria in 68/163 patients (41.7%) and slowing of saccades in 24/ 163 patients (14.7%). *Farid et al*.[24] reported 5/25 patients (20%) with saccadic dysmetria, decreased velocity in 5/25 patients (20%) and prolonged latency in 4/25 patients (16%) using electronystagmography (ENG). Other investigators as *Noffsinger et al*.[32] reported that 40% of their patients had such abnormalities. Similarly, *Williams et al*.[33] and *Grenman*[34] reported such results. Those abnormalities in saccadic eye movement are indicative of brainstem or cerebellar lesion[33,34,35] which matching our inclusion criteria as this type of eye movement place the greatest demands on brainstem and cerebellar circuits controlling gaze[11].

In the present study, smooth pursuit abnormalities were in the form of reduced gain in 32/65 patients (49.2%). Similar to our results, Impaired smooth pursuit in 69/163 (42.3%) of MS patients was reported by *Servillo et al*.[29], also reported in 15/50 MS patients (30%) by *Serra et al*.[11] and in 7/50 patients (14%) by *Downey et al*.[10]. *Jozefowicz-Korczynska* and *Pajor*[36] found that 76.7% of their MS patients had disorders of smooth pursuit using quantitative electrooculography recordings (EOG). Also *Farid et al*.[24] reported 16/25 (64%) of patients with abnormal smooth pursuit in the form of reduced gain. Abnormalities in smooth pursuit are believed to be due to cerebellar lesions[24], thus examination of smooth pursuit system provides a valuable parameter in MS patients to assess brain dysfunction.

Regarding optokinetic abnormalities, in the present study we found 76.9% of MS patients with OKN abnormalities in the form of low gain. Scanty numbers of papers were done to compare with ours except for a study done by *Farid et al*.[24] who reported 56% of MS patients with OKN abnormalities which was lower than that of the pursuit testing. This was not surprising since OKN test is the sum of smooth pursuit system and the saccadic system being less sensitive than smooth pursuit[37].

Pathological tilt of SVV can guide to peripheral and central vestibular pathway originated from brainstem[38] and is used as a marker in acute unilateral vascular lesions[39] and as an index for cerebellar dysfunction[11] which agrees with our assumption that SVV could be used as a feasible oto-neurological tool in MS patients. In our study, 10/65 patients of the study group (6.5%) had abnormal subjective visual vertical. We considered SVV to be abnormal when it exceeded ± 2 degrees of true (gravitational) vertical (0 degrees) even in one direction. Three of the ten patients with abnormal SVV were with cerebellar affection, 3 with brainstem affection and 4 with both brainstem and cerebellar affection.

Few studies are available to compare with ours. *Versino et al*.[40] found an abnormal SVV in 20.9% of MS patients. They measured binocularly and did not mention how the normal range was defined. *Serra et al*.[11] found abnormal SVV deviations in 18/50 (36%) of their patients when considering one abnormal condition (both eye viewing or rt. eye viewing or lt. eye viewing) sufficient to be classified as pathological. Although their patients were not examined during MS exacerbations, pathologic tilt of static SVV was common, suggesting underlying damage to central otolithic connections. In their study also, patients with the greatest SVV deviation also had higher Kurtzke FSS scores for cerebellar function and often showed saccadic dysmetria, which indicates involvement of cerebellar connections.

When we compared between study and control groups regarding deviation of SVV on both sides, a highly statistically significant difference was found between the two groups in deviation of SVV toward

right (CW), left side (CCW) and average SVV, similar to our results, *Crevits et al*.[14] reported that the group of MS patients (23 patients) showed significantly larger deviations of SVV than the control group (*P value <0.001*), pathological tilt of SVV being present in almost half of them (48%)

When we tried to find an association between SVV and the EDSS, no statistically significant difference was found. Also, a significant correlation with the disease duration was found with left SVV. Head impulse abnormalities with SVV results and skew deviation abnormalities with SVV revealed no statistically significant difference. Unfortunately, no enough studies to compare with our findings regarding EDSS, disease duration, and cerebellar and brainstem lesions. In the current study we analyzed SVV results in patients diagnosed with cerebellar or/and brainstem lesions, a statistically significant difference found between right SVV abnormalities with cerebellar and brainstem lesions.

CONCLUSION

This study had demonstrated that SVV and oculomotor testing could guide physicians to brainstem and cerebellar lesions in patients with MS. This way could shorten time and proof affordability and feasibility when assessing multiple sclerosis patients with brainstem and cerebellar lesion.

CONFLICT OF INTEREST

There are no conflicts of interest.

REFERENCES

1. Geurts JJ, Barkhof F. Grey matter pathology in multiple sclerosis. J Lancet Neurol 2008; 7: 841–851.

2. Comber L, Galvin R, Coote S. Gait deficits in people with multiple sclerosis: A systematic review and meta-analysis. J Gait & Posture 2017; 51: 25–35.

3. Frischer JM, Weigand SD, Guo Y, Kale N, Parisi JE, Pirko I, *et al*. Clinical and pathological insights into the dynamic nature of the white matter multiple sclerosis plaque. J Ann Neurol. 2015; 78(5):710-21.

4. De Sa JC, Airas L, Bartholome E, Grigoriadis N, *et al*. Symptomatic therapy in multiple sclerosis: a review for a multimodal approach in clinical practice. J Ther Adv Neurol Disord. 2011; 4:139-68.

5. Milo R, Miller A. Revised diagnostic criteria of multiple sclerosis. J Autoimmunity Reviews 2014; 13: 518–524.

6. Alpini D, Caputo D, Pugnetti L, Giuliano DA, Cesarani A. Vertigo and multiple sclerosis: aspects of differential diagnosis. J Neurological Sciences 2001; 22: 84–87.

7. Gelfand JM. Multiple sclerosis: diagnosis, differential diagnosis, and clinical presentation. Handb Clin Neurol; 122: 269-90. Elsevier 2014

8. Tilikete C, Jasse L, Pelisson D, *et al*. Acquired pendular nystagmus in multiple sclerosis and oculopalatal tremor. J Neurology 2011; 76: 1650–1657.

9. Tilikete C, Jasse L, Vukusic S, *et al*. Persistent ocular motor manifestations and related visual consequences in multiple sclerosis. J Annals of the New York Academy of Sciences 2011; 1233: 327–334.

10. Downey DL, Stahl JS, Bhidayasiri R, Derwenskus J, Adams NL, Ruff RL, Leigh RJ. Saccadic and vestibular abnormalities in multiple sclerosis (MS): sensitive clinical signs of brainstem and cerebellar involvement. J Ann New York Acad Sci 2002; 956:438–440.

11. Serra A, Derwenskus J, Downey DL, Leigh RJ. Role of eye movement examination and subjective visual vertical in clinical evaluation of multiple sclerosis. Journal of Neurology 2003; 250: 569–575.

12. Funabashi M, Santos-Pontelli TE, Colafêmina JF, Pavan TZ, Carneiro AA, Takayanagui OM. A new method to analyze the subjective visual vertical in patients with bilateral vestibular dysfunction. J Clinics 2012; 67: 1127–1131.

13. Frisén L. Ocular torsions and the subjective visual vertical with central vestibulo-ocular system lesions: Independence disproved. J Acta Neurologica Scandinavica 2012; 126: 205–209.

14. Crevits L, Venhovens J, Vanoutrive J, Debruyne J. False perception of visual verticality in multiple sclerosis. European Journal of Neurology 2007; 14: 228–232.

15. Brandt T, Dieterich M. Vestibular syndromes in the roll plane: topographic diagnosis from brainstem to cortex. J Annals of Neurology 1994; 36: 337–347.

16. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale. J Neurology1983; 33: 1444-1452.

17. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, *et al*. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. J Ann Neurol 2011; 69: 292-302.

18. Barkhof F, Filippi M, Miller DH, *et al*. comparison of MR imaging criteria at first presentation to predict conversion to clinically definite multiple sclerosis. J Brain 1997; 120: 2059-2069.

19. Tintoré M, Rovira A, Martinez MJ, Rio J, Diaz-Villoslada P, Brieva L, *et al*. Isolated demyelinating syndromes: comparison of different MR imaging criteria to predict conversion to clinically definite multiple sclerosis. AJNR Am J Neuroradiol 2000; 21: 702–6.

20. Bagnato F, Jeffries N, Richert ND, *et al*. Evolution of T1 black holes in patients with multiple sclerosis imaged monthly for 4 years. J Brain 2003; 126: 1782-1789.

21. Bitsch A, Kuhlmann T, Stadelmann C, Lassmann H, Lucchinetti C, Brück W. A longitudinal MRI study of histopathologically defined hypointense multiple sclerosis lesions. J Ann Neurol. 2001; 49(6): 793-6.

22. Huh YE, Kim JS. Patterns of spontaneous and head-shaking nystagmus in cerebellar infarction: imaging correlations. J Brain 2011; 134: 3662-3671.

23. Kobayashi H, Hayashi Y, Higashino K, *et al*. Dynamic and static subjective visual vertical with aging. J Auris Nasus Larynx 2002; 29: 325–328.

24. Farid AS, Shabana MI, Hosni HS, Thabet EM. Assessment of the vestibular function in patients with multiple sclerosis. Egypt J. Neurol. Psychiat. Neurosurg 2004; 41(1): 151-159.

25. Derwenskus J, Rucker JC, Serra A, *et al*. Abnormal eye movements predict disability in MS: two-year follow-up. J Ann NY Acad Sci 2005; 1039: 521–523.

26. Mangabeira-Albernaz PL, Ganança MM, Mangabeira-Albernaz PM, *et al*. Otoneurological aspects in multiple sclerosis. J Acta AWHO 1983; 2: 35–42.

27. Cipparrone L, Fratiglioni P, Siracusa G, *et al*. Electronystagmography in the diagnosis of multiple sclerosis. J Acta Neurol Scand. 1989; 80:193–200.

28. Frohman EM, Frohman TC, Zee DS, *et al*. The Neuro-ophthalmology of multiple sclerosis. J Lancet Neurol 2005; 4: 111-121.

29. Servillo G, Renard D, Taieb G, *et al*. Bedside tested ocular motor disorders in multiple sclerosis patients. J Mult Scler Int. 2014; 2014:732329. doi:10.1155/2014/732329

30. Negm HM, Shabana MI, Shehata HS. Ocular motor tests in relapsing remitting multiple sclerosis. Advanced Arab Academy of Audio-Vestibulogy Journal 2015; 2(1):19-27.

31. Leigh J, Wolinsky J. Keeping an eye on MS. J Neurology 2001; 57:751–752.

32. Noffsinger D, Olsen O, Carhart R, *et al*. Auditory and vestibular aberrations in multiple sclerosis. J Acta Otolaryngol 1972; 303: 1-63.

33. Williams N, Roland P, Yellin W, *et al*. Vestibular evaluation in patients with early multiple sclerosis. Am J Otol. 1997; 18: 93-100.

34. Grénman R. Involvement of the audiovestibular system in multiple sclerosis. An otoneurologic and audiologic study. J Acta Otolaryngol Suppl. 1985; 420: 1-95.

35. Shepard N, Telian S, Smith-Wheelock M, Raj A. Balance disorders in multiple sclerosis; assessment and rehabilitation. J Seminars in Hearing 1990; 11: 292-304.

36. Jozefowicz-Korczynska M, Pajor AM. Evaluation of the smooth pursuit tests in multiple sclerosis patients. J Neurol 2011; 258: 1795–1800.

37. Hain T. Interpretation and usefulness of ocular motility testing. In: Handbook of balance function testing. By; Jacobson, G.; Newman, C.; and Kartush, J. (eds.). Singular publishing group. San Diego. London 1993. Chapter 6: 101-122.

38. Brandt T, Dieterich M. Vestibular syndromes in the roll plane: topographic diagnosis from brainstem to cortex. J Annals of Neurology 1994; 36: 337–347.

39. Brandt T, Dieterich M. Skew deviation with ocular torsion: a vestibular brainstem sign of topographic diagnostic value. J Ann Neurol. 1993; 33: 528-34.

40. Versino M, Colnaghi S, Callieco R, Bergamaschi R, Romani A, Cosi V. Vestibular evoked myogenic potentials in multiple sclerosis patients. J Clinical Neurophysiology 2002; 113: 1464–1469.