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ARTICLE

A disturbed processing of graviceptive pathways may be involved in the pathophysiology of balance disorders in patients with multiple sclerosis

O processamento incorreto das informações graviceptivas pode estar envolvido na fisiopatologia dos distúrbios do equilíbrio em pacientes com esclerose múltipla

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ABSTRACT

The purpose of this study was to determine the relationship between perception of verticality and balance disorders in multiple sclerosis patients. We evaluated patients and healthy controls. Patients were divided into two groups according to their risk of fall, with or without risk of fall, measured by a Dynamic Gait Index scale. Graviceptive perception was assessed using the subjective visual vertical test. Patients with risk of fall showed worse perception than those without risk of fall, $p < 0.001$. Misperception of verticality was correlated with the dynamic gait index scores ($p < 0.001$), suggesting that the larger the error for verticality judgment, the greater risk for falling. Considering that the perception of verticality is essential for postural control, our results suggested that the disturbed processing of graviceptive pathways may be involved in the pathophysiology of balance disorders in these patients.

Keywords: postural balance, multiple sclerosis, vestibular function tests, gravity sensing, sensation disorders, accidental falls.

RESUMO

Nosso objetivo foi determinar a relação entre percepção de verticalidade e alterações do equilíbrio em pacientes com esclerose múltipla (EM). Foram avaliados pacientes e sujeitos saudáveis. Pacientes foram divididos em dois grupos de acordo com o risco de queda, mensurado pelo Índice de marcha dinâmica, formando os grupos com risco e sem risco de quedas. A percepção da verticalidade foi medida através do teste vertical visual subjetiva (VVS). Pacientes com risco de queda apresentaram pior percepção da verticalidade quando comparados aos sem risco, $p < 0,001$. O desempenho no teste da VVS foi pior em pacientes quando comparado aos controles ($p < 0,001$). O erro no julgamento da verticalidade foi correlacionado aos índices de risco de queda ($p < 0,001$), sugerindo que quanto maior o erro no julgamento da verticalidade, maior o risco de queda dos pacientes. Nossos resultados sugerem que alterações das informações em vias graviceptivas podem estar envolvidas nas alterações de equilíbrio dessa população.

Palavras-chave: equilíbrio postural, esclerose múltipla, testes da função vestibular, percepção gravitacional, alterações sensoriais, risco de quedas.

Balance disorders and falls are among the most disabling symptoms in people with Multiple Sclerosis (PWMS) and often are reported as initial symptom of the disease[1,2]. Balance depends on complex interactions among sensorial information such as proprioception, vision and vestibular inputs, adequate integration with multissensorial areas in the CNS and an effective motor system[3,4]. Any deficits on integration of these pathways can damage balance control, increasing the risk of fall[2].

Perception of verticality is an important afferent information for balance control, since it is required for body orientation in space[5,6,7]. Multimodal sensory input is necessary to detect the body verticality in the space. The representation of body schema in the space depends on the proprioceptive signs, provided by sole receptors and joints receptors, and on the detection of gravitational inputs and head position, provided by the otolith organs. The otolith organs

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are gravitational sensors located in the head, called utricle and saccule. Both detect sense of accelerations, including those produced by gravity. The afferents signs provided by the otolith organs are interpreted together with visual and proprioceptive information from head-neck and neck-trunk positions. So, perception of verticality depends on sensors located in the head (otolith organs) and on body sensors[8].

The gravitational perception is frequently measured with the subjective visual vertical (SVV)[9]. SVV test evaluates the ability to adjust a luminous rod in the vertical position in a dark room, without other visual cues[10,11]. Misperception of SVV can reflect damage in peripheral or central vestibular pathways from the brainstem over the thalamus to cerebral cortex[12], or may be a sign of an impaired sensorial integration[13].

Because of the widely distribution of central nervous system (CNS) lesion in PWMS, poor balance control had multifactorial causes that varies from one person to another[14]. Further, some studies suggests that balance disorders in PWMS occurs due to impaired central integration of visual, vestibular, and somatossensorial input[15]. Few previous studies had shown that perception of verticality can be affected in MS patients when compared with healthy controls. Besides that, SVV deviation has also been correlated with disability degree, measured by Expanded Disability Status Scale (EDSS)[16,17]. However, none of these studies has analyzed the correlation between verticality misperception and balance disorders in the PWMS.

Therefore the objectives of this study were: (1) to investigate if perception of visual vertical is different between PWMS with and without dynamic balance disorders and (2) to analyze if misperception of verticality correlates with risk of fall in PWMS.

METHOD

Subjects

We recruited outpatients with relapsing-remitting MS. Patients were included after medical consultation according to the following inclusion criteria: (1) diagnosis of MS according to the McDonald et al.[18] and (2) score of Expanded Disability Status Scale (EDSS)[19] between 0 - 4.5. Patients were excluded if they had (1) relapses over the last 3 months, (2) other neurological diseases, (3) vertigo or vestibular dysfunction, including nystagmus and vestibulo-ocular reflex, (4) cognitive disorders or (5) visual impairment (blindness, blurred vision, diplopia or optic neurits). All patients were under treatment with interferon therapy. Since risk of fall is consequence of balance disorders, patients were divided into two groups according to their risk of fall: risk of fall (RF+) and without risk of fall (RF-), measured by Dynamic Gait Index Scale. Forty-nine healthy controls (HC) were also recruited. They were excluded if they had history of (1) vestibular symptoms, (2) cognitive disorders or (2) severe visual accuracy impairment. All experiments were conducted in accordance with the Declaration of Helsinki and this study was approved by the local Research Ethics Committee. All patients and controls signed the informed consent term.

A total of 98 PWMS (67 females) were included. The EDSS median score in RF- group was 1 (1 - 1,5) and in RF group was 2.5 (2.0 - 3.5). We also evaluated forty nine HC (32 females, age 37.6 ± 7.4).

Clinical assessment of PWMS

Dynamic balance was evaluated by the ***Dynamic Gait Index (DGI).*** This scale was developed by Shumway-Cook et al.[20] to evaluate balance control during walking and to evaluate risk of falling. The measure consist of 8 itens: walk 6 meters, walk and change speed, walk with head turns (look left then right and look up then down), walk with pivot turn, over or around obstacles and going up stairs. The score ranges from 0 to 24. The cut-off point of ≤ 19 was previous established for PWMS to indicate balance disorders and risk of fall by Forsberg et al.[21]. In this study we decided to classify PWMS with balance disorders according to the risk of fall detected by DGI scale. 57 patients had DGI scored higher than 19 point, thus they were included in PWMS group without risk of fall (RF-) and 41 patients were included in PWMS group with risk of fall (RF+), with scores lower than 19 points in DGI scale.

Subjective visual vertical test

The measurement of the SVV was performed in PWMS and HC using a 24 cm long luminous portable rod. The rod was positioned 1.5 meters in front of the subject who was sitting upright and wearing glasses with dark lenses that made use of any other visual reference impossible (Figure 1). Patients remained sitting and the head was aligned with trunk position. Measurements were stopped if the head tilted to either side. Starting the rod from 30 degree oblique position, to clockwise (positive) and counterclockwise (negative) initial positions, the subject verbally instructed the examiner to set the rod into a vertical position. Both, HC and PWMS made ten adjustments, 5 from positive and 5 from negative initial positions. A previous study published by our group used the same methodology to evaluate perception of verticality in patients with Parkinson's disease[22].

Subjective visual vertical calculation

Two different SVV-analyses were performed. In the first analysis the objective was to detect otolithic tonus imbalance, since SVV tilts are known to be a sensitive sign of otolithic tone imbalance and a lesion of the graviceptive pathways. These SVV tilts were calculated as a mean value and expressed as either clockwise or anticlockwise. The values of SVV-deviations from true vertical to the right (clockwise) of the subject examined were considered positive, while deviations to the left (anticlockwise) were deemed negative, and a mean value was calculated, which means that the results should be positive or negative. A second analysis was done to detect intraindividual variability. An

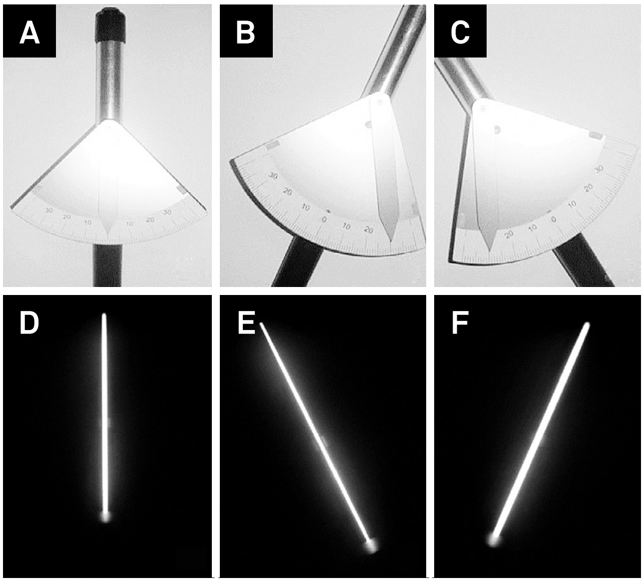

Figure 1. The figure shows the Subjective visual vertical (SVV) test. SVV view of the examiner (A, B, C), and view of the subject (D,E,F). The SVV-deviations from true vertical to the left (anticlockwise) of the subject, were deemed negative (B,E), while deviations to the right (clockwise) of the subject were considered positive (C,F).

intraindividual variability implies a compromised perception of verticality and a disturbed processing of the graviceptive pathways, but not necessarily an otolithic tone imbalance. In this analysis the absolute values of SVV-deviations were considered, which means that we should not considered positive or negative values, since increased shift for either direction of rotation may be symmetrical and a normal mean value may not be representative of abnormal deviations.

Statistical analysis

Data were expressed as means (standard deviation) or median [range], as appropriate. Statistical analysis was performed by the Student t-test to compare EDSS and DGI scores between PWMS groups. Mann-Whitney test to compare the mean of relative and absolute SVV values between PWMS and HC. To compare the differences among each group, RF-, RF+ and control group, the Kruskal Wallis test was performed. Spearman´s correlation test was performed to assess the correlation between SVV values with DGI, considering all PWMS in the same group. The r-values were considered as follows: $r < 0.4$ poor correlation; $0.4 < r < 0.6$ moderate correlation; $r > 0.6$ strong correlation. The level of significance was 5%.

RESULTS

Table shows the demographic and clinical characteristics of the 98 patients according to risk of fall. Disability degree measured by EDSS scale was significantly worse in RF+ group than in RF- group ($p < 0.001$). Patients with risk of fall had a higher EDSS score than the patients without.

Table. Demographic and clinical differences between PWMS with risk of fall (RF+) and without risk of fall (RF-).

Clinical findings	RF+ group n = 41	RF- group n = 57	p-value
Gender, F/M	28 - 13	39 - 18	0.42
Age, years	37.4 (10)	32.5 (8.1)	**0.009**
EDSS score	2.5 [2.0 - 3.5]	1.0 [1.0 - 1.5]	**< 0.001**
Duration disease, years	9.4 (7.1)	6.6 (4.3)	**0.014**
DGI score	22.7 (1.8)	14 (3.4)	**< 0.0001**

Bold p-values are those significant at a 0.05 level. EDSS: Expanded disability status scale; DGI: Dynamic gait index.

Analysis of SVV mean values

In the first analysis, mean SVV-values were considered in order to detect otolithic tonus imbalance. Mean SVV-value in HC was +0.5 (-0.12 - 0.7). In the RF- group the mean SVV-deviation was +0.3º (-0.75 - 1.72), while in the RF+ group it was +0.65º (-1.3 - 1.65). No significant differences were detected between PWMS with and without risk for falling (2-tailed Mann-Whitney test, $p = 0.54$). We did not also find differences in mean SVV-values when we compared PWMS with HC (2-tailed Mann-Whitney test, $p = 0.97$).

Analyses of SVV absolute values

In the second analysis which was done to detect intraindividual variability and the disturbed processing of graviceptive pathways, the SVV absolute values were considered. The absolute mean SVV deviation in HC was 1.2 (0.87 - 1.62), in RF- group was 1.6º (0.97 - 2.3), and in the RF+ group was 2.2º (1.62 - 3.25). Statistical comparison of absolute mean values of SVV proved significant difference between HC, RF- and RF+ (2-tailed Mann-Whitney test, $p < 0.001$, Figure 2). According to our results, misperception of verticality was higher in patients with risk of fall.

Increased misperception of verticality correlates to risk of fall in PWMS

The risk of fall was assessed by DGI scale. The median (range) of DGI score was 24 (21 - 24) in RF- group and 16 (13 - 16) in RF+ group. Since only SVV absolute values were different between groups, we considered these absolute values to correlate with DGI scores. An oposite correlation was found between the SVV absolute values and the DGI-scores ($r_s = -0.325$, $p < 0.001$), suggesting that the larger the error for SVV judgment, the greater the risk for falling (Figure 3).

DISCUSSION

A lot of previous studies have classified PWMS as fallers and no fallers according to their fall history. We chosen to use another method because some of our patients with balance disorders do not report falls since they restrict their diary activity at home, because they feel fear of falling. Thus,

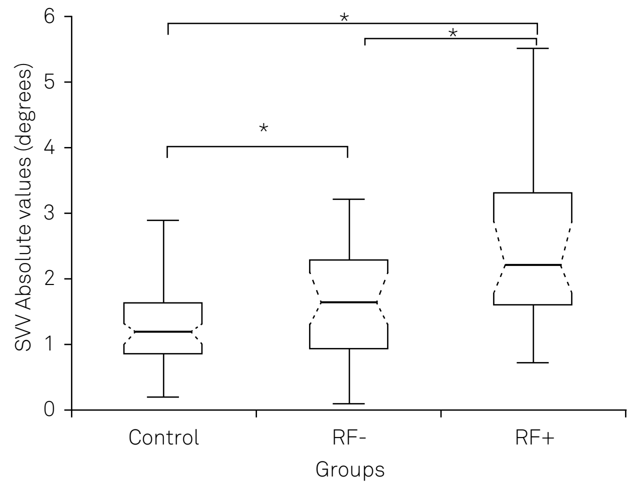

Figure 2. This figure shows the difference of Subjective visual vertical (SVV) test deviation for absolute values among the three groups. The boxes represent the median values, and the first to the third quartiles. The extreme horizontal lines represent the lowest and highest values. Deviation of SVV was larger in MS groups than in the control group ($p < 0.001$).

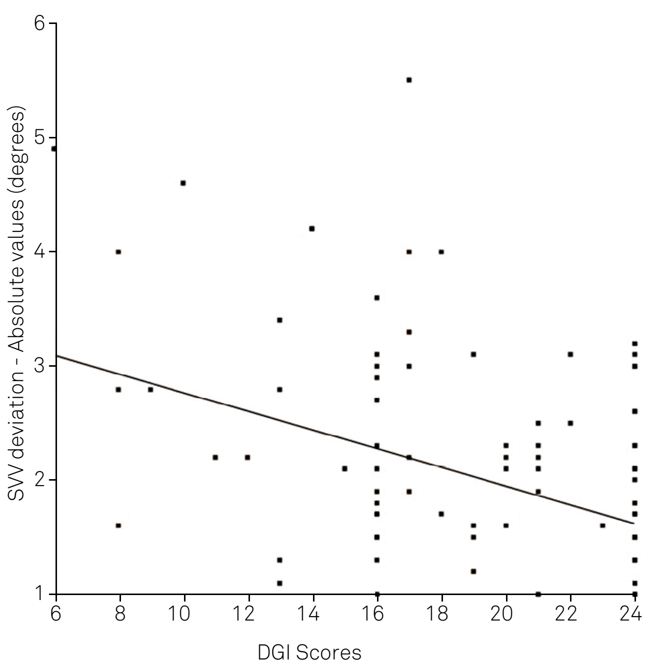

Figure 3. A significant and negative correlation was proved between Subjective visual vertical (SVV) test absolute values and DGI scores in the MS patients group. The results showed that the more risk for falling is correlated with worse perception of verticality. The circles represent the individual SVV deviation in degrees ($p < 0.001$).

the number of fall could not be considered. Our study shows that PWMS with risk of fall have worse misperception of verticality than patients without risk. Moreover, comparing to HC misperception of verticality was also found in patients without risk of fall, suggesting that the misperception of verticality is present even before the clinical manifestation of balance disorders. The misperception of verticality as shown by higher absolute means of SVV deviation, suggesting a disturbed processing of graviceptive pathways, rather than otolithic tonus imbalance.

Only a few previous studies have evaluated the perception of verticality in MS population, and none of them had considered the relationship between misperception of verticality and both dynamic balance disorders or risk of fall. SVV is a test of otolithic function and is able to provide information about the integrity of the vestibular pathways, both peripheral and central[10,11,23]. This suggests that SVV test may be a useful tool for evaluation of vestibular system and sensorial integration[16,17]. The wrong judgment of verticality has been associated with acute unilateral brainstem lesions and thalamic or cortical lesions[12,17,24,25]. In order to assess if the misperception of SVV was related to an otolithic tonus imbalance or a disturbed processing of graviceptive pathways, our study considered two analyses. We found that perception of verticality was different among HC and both PWMS groups, RF+ and RF-, when absolute values of SVV deviation were considered, but not when the arithmetic mean was considered. This finding means that MS patients do not have a graviceptive tone imbalance, but they have an impaired precision of vertical judgment and a defective processing of graviceptive pathways.

The analysis of the SVV test may consider the tilt direction or the intraindividual variability. Intraindividual SVV variability reflects the precision of the rod's adjustment, and is a measure of the precision of vertical perception[26]. So, an increased intraindividual variability is considered to be a decreased effectiveness of the otolithic organs, a disturbed processing of graviceptive pathways with an impaired sensorial integration[13]. Our findings show that even patients without risk of fall have misperception of verticality, probably resulted from impaired central integration, since patients with visual or acute vestibular dysfunction were excluded. We also found that misperception of verticality in MS patients is correlated to the risk for falling evaluated by DGI scale. Prior studies suggested that the incapacity to detect visual verticality could be related to poor balance recover[27,28]. Despite of these studies have evaluated patients that suffered stroke, the findings highlight that some cortical areas are related to perception of verticality, and these sense is not just related to peripheral lesions.

The upright stability requires the determination of body orientation through CNS information and depends on the integration of visual, vestibular and somatosensory inputs, and also an adequate integration of these afferences in the multissensorial cortex areas[4,5]. When the visual information is excluded, the capacity of judgment of gravitational verticality relies on the vestibular system, specifically, the otolithic organs inputs[13,24].

Due to the widespread distribution of lesions in CNS, perception of verticality in MS patients could be affected by the deficient integration of sensorial pathways. Several studies of balance in MS have suggested that impaired central integration seems to be the main mechanism involved with balance deficits[14,15]. Our results suggest that SVV tilt might be a sensitive sign to evaluate impaired afferent pathways related to balance control.

Consistent with our study, Crevits et al.[16] found a positive correlation between SVV tilt and EDSS total scores and concluded that misperception of gravity may interfere with disability. In addition, these authors also found highly significant correlation between SVV deviation and subscores of EDSS for brainstem and cerebellum, associating with dysfunction of oculomotor or otolithic pathways and cerebellar dysfunction. Other authors had also proposed that SVV could be an index for cerebellar dysfunction in MS[16,17]. Our data complement these previous studies because we also found the correlation between disability degree (EDSS) and misperception of SVV. However, we chose not to consider subscores of EDSS. SVV tilt has not been shown to be a cerebellar sign, and the correlation of SVV tilt and cerebellar dysfunction demonstrated by these authors could be probably explained by concomitant brainstem and cerebellar lesions on MS patients.

In our study, we evaluated vestibular function using clinical tests. We included PWMS with normal VOR and without nystagmus positional or evocade. When VOR is abnormal or nystagmus is present, the lesion is characterized by unilateral in peripheral or central vestibular pathways. In these cases, SVV test shows deviation from verticality for ipsiversive or contraversive side from lesions. Because our objective was to analyze the vertical perception which depends on central processing of the vestibular function and visual and proprioceptive functions as well, we excluded patients with vestibular symptoms. Thus, we considered the vestibular clinical tests enough for our purpose. However, we did not use caloric test and this could be a limitation of this study.

Because balance impairment reported as a frequent and disabling consequence of MS, even at the initial stage of the disease, the need for reliable measures to identify subtle impairments that damage balance control is necessary[14]. SVV evaluation proved to be a simple and easy method to detect impairments on central integration areas, even when afferent signs seems normal. Further, the correlation of verticality misperception and impaired DGI scores in MS patients suggests that a disturbed processing of graviceptive pathways may be involved into the pathophysiology of balance disorders in these patients. This finding also suggests that misperception of verticality should be taken into account in rehabilitation programs for prevention of risk of falls and improve balance strategies in MS patients.

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