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White matter lesions and vascular vertigo: clinical correlation and findings on cranial magnetic resonance imaging

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Abstract. – OBJECTIVE: Vestibular disorders and anxiety are closely related, probably because they share some neuronal pathways. Ageing and patient comorbidities are important facilitating factors, and multiple vascular risk factors could contribute to the onset of a vestibular syndrome called vascular vertigo. White matter lesions (WMLs) are often seen on magnetic resonance imaging (MRI) scans of elderly people and are related to various geriatric disorders, including dizziness. The cause of this correlation could be the disruption of neuronal networks that mediate higher vestibular cortical function. Numerous neuronal pathways link the vestibular network with limbic structures and the prefrontal cortex modulates anxiety through its connections to the amygdala. These could also explain nausea and sickness. The aim of the present work was to investigate the correlation between WML, vascular vertigo and cognitive functions.

PATIENTS AND METHODS: Our team at the Poliambulanza Foundation Hospital of Brescia studied 90 patients (mean age 75 years) suffering from vascular vertigo with positive WML on MRI, by mapping the lesions and by grading anxiety and sickness symptoms. Furthermore, the same patients were treated with sulodexide (a glycosaminoglycan with antithrombotic activity) for 90 days (500 LSU/day for the first 45 days and 250 LSU/day for the following 45 days) to evaluate the efficacy on the vestibular symptoms.

RESULTS: The results showed that the most frequent WML sites were frontal (n=34) and capsule (n=30) areas. Patients had a significant improvement on anxiety and sickness scores (p=0.0001 and p=0.02 respectively) after sulodexide treatment.

CONCLUSIONS: In patients with vascular vertigo we confirmed the correlation between dizziness and anxiety and showed preliminary data regarding the efficacy of sulodexide in relieving in these patients anxiety and sickness.

Key Words
White matter lesions, Vascular vertigo, anxiety, Sulodexide.

Introduction

Good balance is necessary in order to execute motor skills and to safely deal with the demands of daily life[1]. Vestibular disorders are characterized by a combination of perceptual, oculomotor, postural and vegetative manifestations, which cause the symptoms of vertigo, nystagmus, ataxia and nausea[2]. Dizziness has long been considered a "simple" somatoform manifestation in patients who do not experience a true rotational vertigo. Dizziness could be described as an individual experience that is also affected by emotional factors; thus, different patients may describe their sensations in different ways[1,3,4].

The traditional classification of vestibular disorders is based on the anatomical site of the lesion and distinguishes between the peripheral and the central vestibular system. This classification could not reflect the clinical syndrome, which may involve both the peripheral and the central vestibular system, leading to "higher vestibular function" disorders, since inputs from visual, vestibular and proprioceptive systems are integrated and elaborated through cognitive functions[2,5]. Numerous polysynaptic pathways link the vestibular network with limbic, hippocampal, cerebellar and cerebral cortex structures in order to mediate higher cognitive functions[2]. The vestibular system provides the brain with sensory signals for postural and oculomotor control, as well as for spatial and body perception and cognition[5]. Additionally, a central lesion, such as cerebellar infarctions, may mimic a peripheral disorder and could be misinterpreted[2,6].

Vestibular disorders lead to a significant degree of handicap and emotional disturbance for the patient[7]. In the first days after an acute vestibular deficit, motor and spatial learning become very important to facilitate recovery of the bal-

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ance function. In addition, new features emerge during this period, with implications on psyche, behavior and emotions[5].

Vestibular disorders and anxiety appear to be closely related[8]. Vertigo and dizziness are common symptoms in patients with anxiety, sickness and imbalance[1,3,4]. On the other hand, the combination of unpredictable vertigo attacks and accompanying severe vegetative reactions contributes to increase anxiety and fear[5]. Recent report considered that during the first vertigo attack 93% of patients have a fear of serious illness and 35% have panic[5]. Anxiety and fear increase in places with a rich visual surrounding and where movements require good head-eye coordination. Furthermore, anxiety is probably one of the most important causes preventing adaptation[1,4]. The relation between anxiety and vestibular disorders could be explained by the fact that they share some neural pathways. This could lead to a vicious circle where dizziness and anxiety increase each other[8]. Dizziness affects about 30% of people over the age of 65[9,10]. With increasing age, a progressive loss of function of the vestibular, visual and proprioceptive systems can lead to balance problems[9]. Patient comorbidities also play an important role in aggravating the physiological degeneration of the balance system. For example, cardiovascular comorbidities are correlated to both peripheral and central vertigo[6,11-13]. The most important cardiovascular risk factors are: hypercholesterolemia, cardiac disease, diabetes mellitus, arterial hypertension and carotid atherosclerosis[14]. 4-years and 9-years follow-up studies also showed that subjects suffering from vertigo have a higher risk of stroke than the general population[15,16]. Multiple vascular risk factors could contribute to the onset of a vestibular syndrome called vascular vertigo due to its vascular etiology[14,17,18].

The areas in cerebral white matter that appear hyperintense on T2-weighted Magnetic Resonance Imaging (MRI) and hypointense on computed tomography are commonly referred to as white matter lesion (WML)[19,20]. WMLs are attributed to degenerative changes of small vessels and of long penetrating arteries and are implicated in the pathogenesis of cognitive decline and dementia[21-23]. Currently, WMLs are divided into periventricular white matter lesions, which are attached to the ventricular system, and deep white matter lesions, located in subcortical regions [20,24]. WMLs are often seen on MRI scans of elderly people and are related to various geriatric disorders, including cerebrovascular diseases, cardiovascular diseases, dementia, and psychiatric disorders[19,25-28]. MRI features of WML are correlated with dilatation of perivascular spaces, especially in the frontal and parietal subcortical white matter[21,24]. A large meta-analysis of 46 observational studies[28] demonstrated that WMLs are associated with greater risk of future stroke, dementia and mortality. There is evidence that periventricular white matter lesions are particularly related to cognitive decline, whereas subcortical white matter lesions may be related to late onset depression[21]. In a cohort study, the presence of thalamic lacunes was associated with poor global cognitive performance, low motor activity and poor executive function performance; moreover, the presence of lacunes in the pallidum or putamen was associated with memory dysfunctions[29,30]. Above all, deep brain infarcts have been associated with vascular cognitive impairment, including cognitive decline and dementia[30]. Although we know the association of WML, cognitive decline, aging, vascular risk factors, and actual dementia, the primary underlying mechanism of these processes is still unclear[31]. WMLs are also associated to gait disturbance and dizziness[30,32,33]. In a group of older patients suffering from subjective and objective abnormalities of gait and balance of unknown cause, Baloh et al[32] found a significant (p<0.01) more severe subcortical WML on MRI when compared with an age- and sex-matched control group. Additionally, a retrospective case analysis showed increased severity and frequency of WML in subjects with unexplained dizziness, suggesting that WML could contribute to the development of dizziness[33]. The cause of this relation between WML and vestibular disorders is still unclear and may involve several mechanisms. Lesions could interfere with the central processing of sensorimotor signals leading to impaired postural responses or may cause a disconnection syndrome involving vestibular or locomotor areas of the brain[32,33]. Indeed, the human brain contains multiple neuronal networks that serve motor and neurobehavioral functions such as visuospatial ability, complex cognition, and emotion. WML might disrupt higher vestibular cortical functions involved in these networks. WML disease could be especially critical later in life, because white matter volume might decline with age more than gray matter volume[20].

We systematically studied dizzy patients with MRI to map WML and to verify the correlation between WML and vestibular disorders, in particular vascular vertigo. Reported below are our case load, neuroradiological features and out-

comes in managing dizziness in elderly patients at the Poliambulanza Foundation Hospital of Brescia, Italy.

Patients and methods

A total of 90 patients (53 females and 37 males), with a mean age of 75 years (range 59-89 years), were observed from January 2014 to January 2015. All patients underwent a clinical vestibular examination. Based on clinical suspicion and investigation results they also underwent 1.5 T Cranial MRI. All patients showed at least 1 WML on MRI, had been suffering from imbalance for a minimum period of one year and had a diagnosis of vascular vertigo based on at least 3 of the following vascular risk factors: cerebrovascular diseases; carotid disease; ischemic heart disease; diabetes mellitus; arterial hypertension; arteriopathy; family history of vascular diseases; smoking; alcohol consumption; obesity; fibrinogen >350 mg/dl; triglycerides >180 mg/dl; cholesterol >220 mg/dl. Patients with cognitive impairment and psychiatric or neurological diseases were excluded. After informed consent had been obtained, the patients were treated with sulodexide, glycosaminoglycans with antithrombotic activity used in dizziness of vascular etiology[14,17,18,34-36]. Patients were given two capsules of sulodexide 250 LSU (500 LSU/die) for the first 45 days, one in the morning and one in the evening. After 45 days, sulodexide was reduced to one capsule each morning (250 LSU/die). Patients were evaluated according to changes in symptoms and clinical presentation of anxiety, sickness and imbalance measured by scores at the end of 30 (1 month), 60 (2 months) and 90 days (3 months).

Table I. Vascular risk factors.

Vascular risk factors		
Risk factors	**No. of patients/90**	**%**
Arterial hypertension	73	81%
Hypercholesterolemia	60	67%
Hypetriglycerydemia	40	44%
Peripheral arterial disease	38	42%
Cardiac disease	35	39%
Diabetes mellitus	30	33%
Cerebrovascular events	15	17%

Total is >90 because patients can have more than one risk factor.

Statistical Analysis

For the statistical analysis we used a symmetry test (Pearson's Median Skewness) and the *p*-value <0.05 was considered statistically significant.

Results

All 90 patients (100%) completed the entire 90-day observation period. Vascular risk factors are outlined in Table I. 81% of patients had arterial hypertension, 67% had hypercholesterolemia and about 40% had hypetriglyceridemia. 15 patients out of 90 (17%) had already experienced cerebrovascular events.

Figure 1 shows the anatomical distribution of the WML. The most frequent sites are the frontal and capsule areas, where lesions were present in 34 and 30 cases respectively.

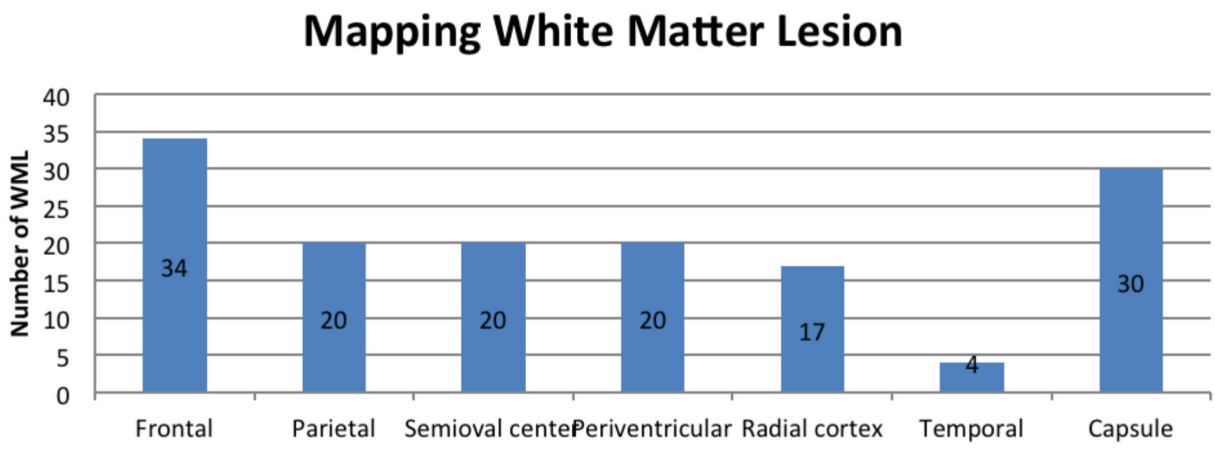

Figure 1. Anatomical distribution of WML. The figure shows the frequency of mapped WML in the different anatomical regions in 90 patients suffering from vascular vertigo. The total number of lesions is greater than the number of patients (90) because one patient can have more than one lesion.

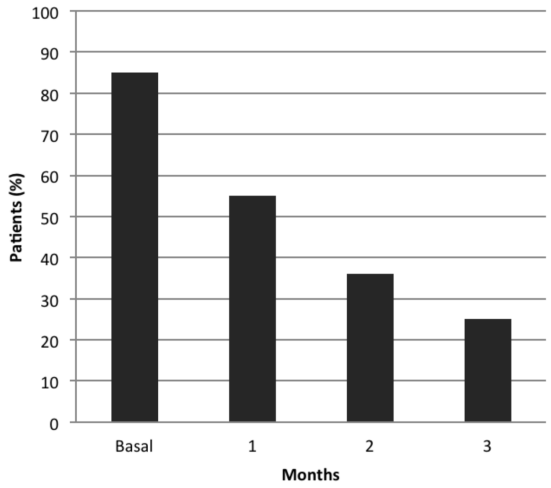

Figure 2. Anxiety score variation during sulodexide treatment. The figure shows the serious anxiety score variation at different times (months) in patients with vascular vertigo and positive WML, treated with sulodexide for 90 days (p<0.05).

At basal, patients showed 85% of serious anxiety score and 35% of serious sickness. The analysis of the scores observed before and after sulodexide treatment showed statistically significant differences for anxiety (p=0.0001) (Figure 2) and sickness (p=0.02) (Figure 3), while the difference for imbalance was not significant (p=0.6) (data not shown). In particular, after 3 months of sulodexide treatment, serious anxiety was 25% and serious sickness was 5%, with a reduction of 60% and 30% respectively.

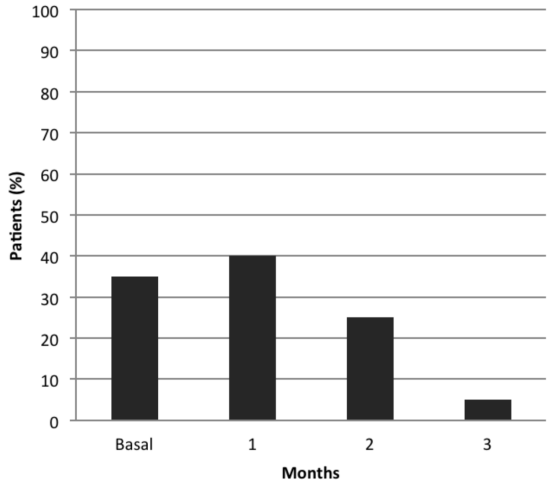

Figure 3. Sickness score variation during sulodexide treatment. The figure shows the serous sickness score variation at different times (months) in patients with vascular vertigo and positive WML, treated with sulodexide for 90 days (p<0.05).

Discussion

The present study has investigated the correlation between WML, vascular vertigo and cognitive functions.

As seen in Figure 1, we found a high prevalence of frontal and capsule WML in patients suffering from vascular vertigo. Frontal and prefrontal WML could be associated with both vestibular disorders and anxiety. Many authors have proposed the existence of a "vestibular cortex". In humans, galvanic and caloric vestibular stimulation activates several frontal cortical regions[5]. Furthermore, studies on animals have focused on structures that receive vestibular inputs and are located in frontal, temporal and parietal cortex[37,38]. Acute lesions of these areas, for example after middle cerebral artery infarctions, cause tilts of perceived vertical, body lateropulsion and rotational vertigo. The vestibular cortex intimately interacts with the visual cortex to match the two 3-D orientation maps and mediates self-motion perception[37,38].

In our case load, the scores recorded pre- and post-treatment with sulodexide showed a significant improvement with regard to anxiety (p=0.0001) and sickness scores (p=0.02) (Figures 2 and 3), probably due to the hemorheologic activity of sulodexide. The difference for imbalance score was not significant (p=0.6) but this result was expected because subjects were chronic patients with high clinical complexity. Numerous neuronal pathways link the vestibular network with limbic and hippocampal structures[2]. These structures are involved in the fear network model, which exhibits aberrant activation patterns in a variety of anxiety disorders. In particular, the prefrontal cortex modulates anxiety and other emotional behaviors through its connections to amygdala[39]. Kim et al[39] found alterations in frontal WM and WM around the frontal lobe in patients with panic disorders. Furthermore, abnormal levels of anxiety have been observed in patients suffering from vestibular deficit[5,8]. These neuronal connections with limbic structures could also explain nausea and sickness, which are common symptoms in patients with vestibular syndromes[1,2,5]. Based on the consideration that WML and vascular vertigo could have a vascular pathophysiolo-

gy, the pharmacological intervention to improve vascular homeostasis could relieve symptoms of anxiety and sickness.

Conclusions

Vestibular disorders and anxiety are intimately related and this relationship could be explained by the fact that they have some common neural pathways. The correlation could be further supported by the high prevalence of frontal WML among people with vestibular disorders and anxiety. Cardiovascular factors could have a pathogenetic role in WML as well as in vestibular disorders and in aggravating symptoms of both diseases. Our case load with patients suffering from vascular vertigo confirmed these correlations and assessed interesting preliminary data regarding the efficacy of sulodexide in relieving anxiety and sickness symptoms in these clinically complex patients.

Conflict of interest

The Authors declare that they have no conflict of interests.

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