

Retinal nerve fiber layer thickness and visual aura mechanism in patients with vestibular migraine with or without white matter lesions

^{1,2}Yu Shen, ³Defu Li, ⁴Mengyao Hu, ¹Qian Cao, ¹Zhou Hou, ¹Lijun Xu

¹Department of Neurology, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi; ²Department of Neurology, The First Affiliated Hospital of Nanchang University, Nanchang, Jiangxi; ³School of Public Health, Nanchang University, Jiangxi Provincial Key Laboratory of Preventive Medicine, Nanchang, Jiangxi; ⁴The Medical Imaging Center, The Second Affiliated Hospital of Nanchang University, Nanchang, Jiangxi, China

Abstract

Background & Objective: The pathogenesis of vestibular migraine (VM) is still unclear. A considerable proportion of patients with VM have white matter lesions (WMLs). We sought to determine whether the presence of WMLs was related to the thickness of the retinal nerve fiber layer (RNFL) in VM patients. We also investigated the relationship of visual aura to the thickness of the RNFL and explored the possible mechanisms of visual aura. **Methods:** This study was a large single-center, prospective, controlled study. A total of 50 patients with VM with or without visual aura and 50 healthy controls were recruited. We assessed WMLs using cranial magnetic resonance imaging (MRI) and measured RNFL thickness using optical coherence tomography (OCT). The relationship between RNFL thickness and WMLs was analyzed. RNFL thicknesses for the aura group, non-aura group and control group were compared. **Results:** (1) The RNFL of the VM group was significantly thinner than that of the control group. (2) When VM patients were divided into two groups based on the presence or absence of WMLs, the RNFL of VM patients with WMLs was significantly thinner, while the RNFL of VM patients without WMLs was significantly thicker, than that of the controls. (3) When the VM group with WMLs was subdivided into two groups according to the presence or absence of visual aura, we found no significant difference in the RNFL thickness of the subgroups with and without visual aura. However, the RNFL thickness of the control group was significantly greater than that of the VM with WML groups with or without visual aura. (4) Finally, when the VM group without WMLs was subdivided into two groups according to the presence or absence of visual aura, there was no significant difference between the RNFL thicknesses of the 2 subgroups. The RNFL thickness of VM patients without WMLs with and without visual aura was greater than that of the control group. **Conclusion:** Among VM patients, RNFL thinning is positively correlated with the presence of WMLs, while visual aura symptoms are not significantly related to RNFL thickness, indicating that the mechanism of visual aura may not be a disorder of the vascular system. If WMLs develop in VM patients in the future, repeated assessment to look for an associated decrease in RNFL thickness may be helpful.

Keywords: Vestibular migraine (VM), retinal nerve fiber layer (RNFL), white matter lesions (WMLs), visual aura

INTRODUCTION

Vestibular migraine (VM) is a central vestibular disease¹ that mainly manifests as recurrent spontaneous positional vertigo and migraine symptoms.² In recent years, VM has been identified as a primary cause of vertigo and a major cause of after benign paroxysmal positional vertigo (BPPV).³ Approximately 7% of adult patients in dizziness clinics have VM.⁴ This

disease has received increasing attention from scholars who study vertigo. Its pathogenesis is thought to be related to genetic factors, cortical spreading depression, a disordered relationship between brainstem and trigeminal input structures, and dysregulation of the neurovascular system⁵⁻⁸, but the specific mechanisms are unclear.

Efforts to confirm the possibility of a disordered neurovascular state in VM can guide treatment

Address correspondence to: Professor Lijun Xu, Department of Neurology, The Second Affiliated Hospital of Nanchang University, No. 1, Minde Road, Nanchang, Jiangxi, China. E-mail: xulijun20050901@sina.com

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of the disease. Previous studies have suggested a relationship between migraine and vascular events, resulting in hyperintense subcortical signals on T2-weighted brain magnetic resonance imaging (MRI) scan due to chronic ischemia.⁹⁻¹¹ The hypothesis that chronic ischemia is present in migraine can be investigated by studying the retinal nerve fiber layer (RNFL) because there is a close anatomical relationship between the blood supply to the brain and the retina, and both vascular networks have similar vascular regulatory processes.¹²⁻¹⁵ No previous studies have explored the relationship of WMLs and the RNFL to VM, so in doing this, we wanted to look for evidence of a vascular pathogenesis for VM.

In this study, we used optical coherence tomography (OCT) to assess whether RNFL thickness was related to the presence of WMLs in the brains of VM patients. We sought to determine if VM was related to RNFL thickness and the presence of WMLs and to assess the relationship of visual aura with the thickness of the RNFL and the presence of WMLs.

METHODS

This was a single-center prospective study. It was carried out at the Second Affiliated Hospital of Nanchang University. This Hospital has a clinic specializing in dizziness to provide medical and health services for 50 million people in the province. From September 2019 to July 2021, we screened patients experiencing dizziness who were treated by or referred to the neurology and otolaryngology departments. Among them, 50 VM patients with or without aura who met the diagnostic criteria in the third edition of the International Classification of Headache Disorders (ICHD-3)¹⁶ and 50 sex- and age-matched healthy controls recruited from the community were selected. The specific diagnostic criteria for VM are as follows: (1) five episodes of vestibular symptoms lasting from 5 minutes to 72 hours; (2) the presence of a history of migraine with or without aura (according to ICHD diagnostic criteria); and (3) at least 50% of the vestibular symptoms exhibiting one or more of the following migraine features: ① 2 of 4 of unilateral headache, pulsating, moderate to severe pain and worsening with physical activity ② phobias of sound and light; ③ visual auras; and (4) not better accounted for by other vestibular diseases or migraine. However, for this study, we only selected patients with visual auras, and patients with other types of auras were excluded. All participants underwent

MRI head scans to check for the presence of WMLs, and OCT scans were performed to obtain RNFL thickness measurements. The study was approved by the ethics committee of the Second Affiliated Hospital of Nanchang University, and the study was carried out in full accordance with the principles of the Helsinki Declaration, with the informed consent of patients and healthy controls.

Patients with any headache or type of vertigo other than VM were excluded, including types of headache or vertigo associated with hypertension, diabetes, cardiovascular disease, stroke, encephalitis, head trauma, benign vertigo, vestibular neuritis, brainstem infarction, epilepsy, and vestibular paroxysmia. The control group was required to have no headache or vertigo (fewer than 3 instances in the past year) and any individuals with WMLs found by a brain MRI for other reasons were excluded. In addition, all participants had to undergo a complete ophthalmic examination, including intraocular pressure measurement, best-corrected visual acuity testing and slit lamp examination. A professional ophthalmologist independently excluded patients with elevated intraocular pressure, secondary glaucoma, cataract or corneal opacity, high myopia (spherical equivalent less than or equal to -6.0 dioptres) and previous ophthalmic surgery. The study included patients aged 18-70 years to avoid confounding issues from incomplete eye development in younger patients, and unpredictable degeneration of various eye structures in older patients. All patients underwent an OCT (CIRRUS HD OCT; SINGAPORE) examination. The assessment of RNFL thickness comprised three continuous circular scans with a diameter of 3.4 mm centered on the right optic disc. The average RNFL thickness was used as the final value. Patients with a difference in RNFL thickness greater than 20 μ m between the left and right eyes were excluded from this study.

WMLs were diagnosed with 3T brain MRI. The Fazekas scale¹⁷ was used to evaluate the paraventricular and deep white matter with fluid-attenuated inversion recovery (FLAIR) on T2-weighted imaging, respectively. The absence of any lesions in the paraventricular region was indicated as '0'; cap-shaped or pencil-like thin layer lesions were represented by a '1'; smooth halo lesions were rated as '2'; and irregular high signal extending into deep white matter was scored as '3'. A deep white matter score of 0 indicated the absence of disease; a score of 1 point indicated punctate disease; 2 points indicated merging lesions; and 3 points indicated a large

area of fusion. The total score range is 0 to 6, divided into paraventricular and deep regions, each region having a maximum score of 3. (The specific scoring criteria are shown in Figure 1).

Patients with secondary WMLs or hereditary WMLs were also excluded from the experiment. Fortunately, no such patients were identified in this study. The assessments were independently completed by two senior radiologists. In cases of disagreement, a third senior radiologist provided a deciding opinion.

Statistical analysis

The statistical analysis included 100 subjects, consisting of 50 VM patients and 50 healthy controls. For the purpose of the experiment, we made multiple comparisons. First, we compared the RNFL thickness in VM patients and normal controls. Then the VM group was divided into VM patients with WMLs and those without WMLs. These 2 groups were further subdivided according to the presence or absence of visual auras into 4 subgroups: i) VM patients with visual auras and WMLs, ii) VM patients with visual auras without WMLs, iii) VM patients with WMLs without visual auras and iv) VM patients without visual auras or WMLs. All groups underwent evaluation of the average thickness of the RNFL in the right eye via OCT. Analysis of variance was used to assess the differences between the groups, and Tukey's post-hoc test was used to determine the source of the differences. Statistical significance was set as $P < 0.05$. All statistical analyses were performed using IBM SPSS statistics 25.0 software (SPSS, Chicago, IL, USA).

RESULTS

The average age of the VM patients was 46.92 ± 14.38 years, and there were 9 males (18%) and 41 females (82%). The average age of the healthy controls was 49.52 ± 13.39 years, and there were 13 males (26%) and 37 females (74%). Among the 50 VM patients, 23 (46%) had visual auras, and 27 (54%) had no visual auras. 34 (68%) patients had WMLs on MRI, and 16 (32%) had no evidence of WMLs. There was no significant difference in sex or age between the VM patients and the healthy controls. The average RNFL thickness of all the groups is shown in Table 1.

Grade 1 WMLs accounted for the vast majority (26, 76.5%) of patients; 6 (17.6%) patients had grade 2 WMLs, and only 2 (5.9%) patients had grade 3 WMLs. We thought that subgrouping such a small number of patients would not yield meaningful results. Thus, we combined all patients with any grade of WML for statistical analysis.

First, we performed a statistical analysis comparing all VM patients with healthy controls. We found that the RNFL in the VM patients was significantly thinner than that in the controls ($P = 0.017$). Then we divided the VM patients into two groups according to the presence or absence of WMLs and compared them with the healthy control group. These three groups were compared using analysis of variance and Tukey's post-hoc test. There were significant differences among the three groups ($P < 0.001$) (Table 2 and Figure 2). The RNFL of the VM patients without WMLs was thicker than that of the healthy controls. As expected, the RNFL of the VM patients with

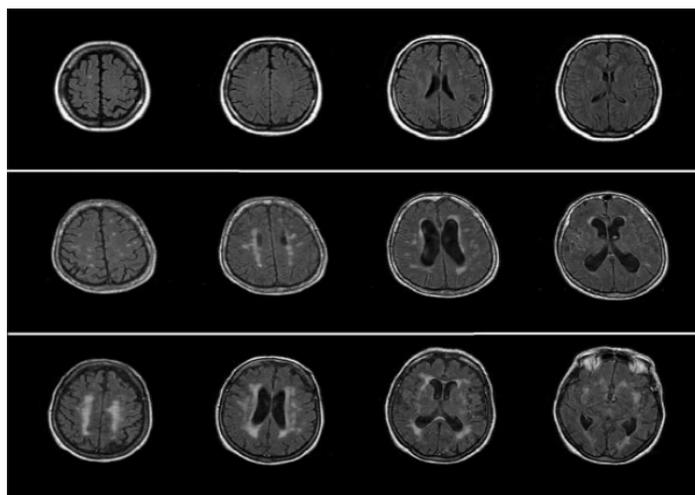


Figure 1. The first row shows brain images with a score of 0 or 1, the second row, images with a score of 2, and the third row, images with a score of 3.

Table 1: Average retinal nerve fiber layer (RNFL) thickness and sample size for all groups

Group	n	Mean RNFL (micron)	SD	SE
VM-WML absent	16	111.25	7.53	1.88
VM-WML present	34	95.41	7.54	1.29
VM	50	100.48	10.55	1.49
Control	50	105.16	8.57	1.21
VM-WML present and aura absent	16	97.94	4.12	1.03
VM-WML present and aura present	18	93.17	9.17	2.16
VM-WML absent and aura absent	11	109.09	6.17	1.86
VM-WML absent and aura present	5	116.00	8.75	3.91

VM: vestibular migraine; WML: white matter lesions; SD: standard deviation
SE: standard error; RNFL: retinal nerve fiber layer

WMLs was the thinnest among the three groups.

We then sought to determine if visual aura symptoms were related to the thickness of the RNFL. From the 34 patients with WMLs (68%) in the VM group, 18 patients with visual aura and 16 patients without visual aura were compared with the healthy control group. The RNFL thickness of the three groups was compared by analysis of variance. No significant difference in RNFL thickness was found between patients with WMLs without visual aura and those with WMLs and visual aura ($P = 0.089$). However, the RNFL of the control group was significantly thicker than that of the WML group as a whole ($P < 0.001$) (Table 3 and Figure 3). From the 16 patients (32%) with VM without WMLs, 5 patients with aura and 11 patients without visual aura were compared with the healthy control group. The RNFL thickness of the three groups was assessed with analysis of variance. The RNFL thickness of the subgroup without WMLs with visual auras was not significantly different from that of the subgroup without WMLs and without visual auras

($P = 0.125$). The RNFL of the subgroup without WMLs with visual auras was significantly thicker than that of the control group ($P = 0.007$) (Table 4 and Figure 4).

DISCUSSION

This study aimed to explore the correlation between RNFL thickness and WMLs in VM patients. WMLs have always been regarded as a characteristic result of chronic ischemic injury, and RNFL thickness is thought to be correlated with the presence of WMLs.¹⁸ We thus wanted to use RNFL thickness as an objective indicator to determine the relationship of VM and visual auras to chronic ischemia. The results confirmed a relationship between RNFL thinning and WMLs in VM patients. The RNFL of VM patients was significantly thinner than that of the healthy controls. Moreover, the RNFL of the VM patients with WMLs was significantly thinner than that of the VM patients without WMLs. Visual aura symptoms were not correlated with

Table 2: Tukey post hoc test results (VM)

Group A	Group B	Mean difference (A -B)	SE	P value
VM-WML absent	VM-WML present	15.84*	2.45	<0.001
	Control	6.09*	2.32	0.01
VM-WML present	VM-WML absent	-15.84*	2.45	<0.001
	Control	-9.75*	1.79	<0.001
Control	VM-WML absent	-6.09*	2.32	0.01
	VM-WML present	9.75*	1.79	<0.001

Results from multiple comparisons between VM patients with white matter lesions (WMLs), VM patients with no WMLs, and the control group for right eye average retinal nerve fiber layer (RNFL) thickness detected by optical coherence tomography.

*Mean difference is significant at the 0.05 level.

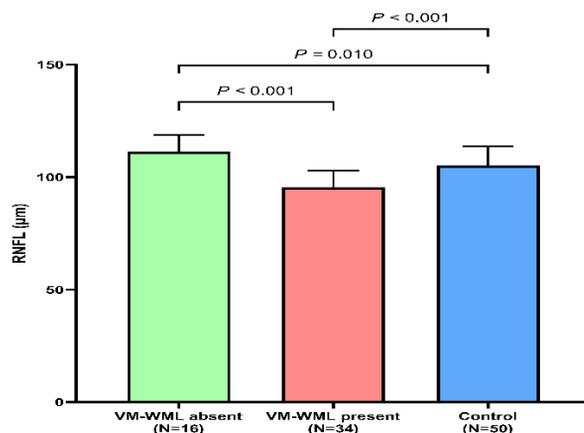


Figure 2. Three-color bar chart showing the number of each subgroup, the average RNFL thickness and the p value of component comparison.

RNFL thickness in VM patients. To the best of our knowledge, this study is the first to explore the relationship between RNFL thickness and the presence of WMLs in VM patients.

Histology and embryology have shown that the retina is an extension of the diencephalon. During embryonic development, they share the same vascular origin.¹⁹ The vascular supply of the brain and that of the retina are closely related and have the same regulatory processes.¹⁹⁻²³ A large number of previous studies have indicated that the retina and brain structure of migraine patients show a thinner RNFL and the presence of WML respectively, and a correlation between the two has also been demonstrated.^{24,25} Many theories suggest that migraine and vertigo are closely related.²⁶ Most hypotheses of VM pathogenesis propose that VM is a subset of migraine.^{1-2,27}

Previous studies have suggested that visual aura symptoms occur because of cortical spreading depression and/or trigeminal neurovascular dysfunction.^{6-7,28} Cortical spreading depression is considered to be a transient depolarization

of a large number of neurons with inhibition of bioelectrical activity.⁶ The theory of trigeminal neurovascular dysfunction is that the contraction or relaxation of blood vessels leads to changes in vascular permeability, resulting in transient ischemia and hypoxia. When such changes occur in the retinal arteries, a visual aura occurs. Recurrent ischemia and hypoxia then leads to long-term ischemic changes, that is, to changes in WMLs and RNFL thickness.⁷ However, our findings do not support the vascular dysfunction hypothesis. Aura symptoms are not associated with thinning of the RNFL. On the contrary, in the group without WMLs, the RNFL of VM patients with visual aura symptoms is thicker than in controls. A previous study has also found that in migraine patients, the presence or absence of visual aura did not cause significant changes in RNFL.²⁹ We therefore believe that visual auras are better explained by cortical spreading depression.

In our study, 68% of VM patients had WMLs. Does this mean that the occurrence of VM is related to ischemia and hypoxia? We cannot

Table 3: Tukey post hoc test results (VM-WML present)

Group A	Group B	Mean difference (A -B)	SE	P value
VM-aura absent	VM-aura present	4.77	2.77	0.089
	Control	-7.22*	2.32	0.003
VM-aura present	VM-aura absent	-4.77	2.77	0.089
	Control	-11.99*	2.22	<0.001
Control	VM-aura absent	7.22*	2.32	0.003
	VM-aura present	11.99*	2.22	<0.001

Results from multiple comparisons between VM-WML present patients with visual aura, VM-WML present patients with no visual aura, and control group for right eye average retinal nerve fiber layer (RNFL) thickness detected by optical coherence tomography.

*Mean difference is significant at the 0.05 level.

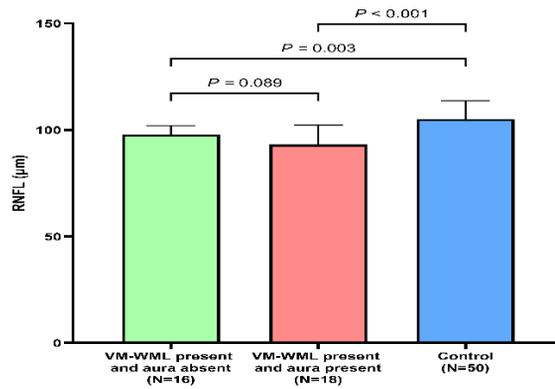


Figure 3. Three-color bar chart showing the number of each subgroup, the average RNFL thickness and the p value of component comparison.

Table 4: Tukey post hoc test results (VM-WML absent)

Group A	Group B	Mean difference (A – B)	SE	P value
VM-aura absent	VM-aura present	-6.91	4.45	0.125
	Control	3.93	2.75	0.157
VM-aura present	VM-aura absent	6.91	4.45	0.125
	Control	10.84*	3.87	0.007
Control	VM-aura absent	-3.93	2.75	0.157
	VM-aura present	-10.84*	3.87	0.007

Results from multiple comparisons between VM-WML-absent patients with visual aura, VM-WML-absent patients with no visual aura, and the control group for right eye average retinal nerve fiber layer (RNFL) thickness detected by optical coherence tomography.

*Mean difference is significant at the 0.05 level.

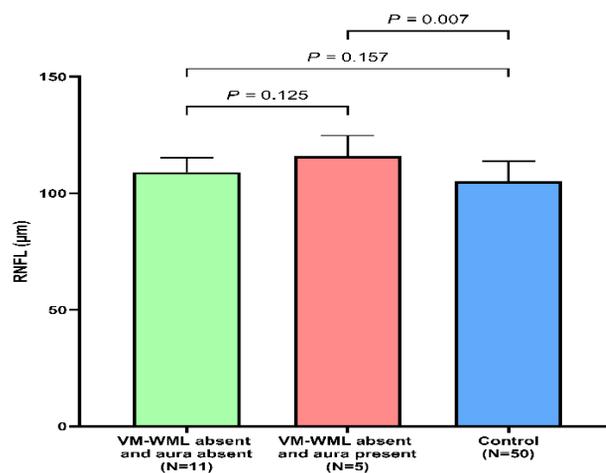


Figure 4. Three-color bar chart showing the number of each subgroup, the average RNFL thickness and the p value of component comparison.

form a definitive conclusion. Although many VM patients have WMLs and thinning of the RNFL, there are still a large number of patients without WMLs. This prospective study attempts to eliminate known confounding factors for WMLs and RNFL thickness, but there are still certain limitations: 1. This study initially was designed to grade WMLs; it was ultimately unsuccessful because the sample sizes of Grade 2 and 3 WMLs were too small, and it was not possible to explore whether more extensive WMLs were correlated with a thinner RNFL. 2. Although recruitments of VM patients were carried out over two years, our sample size remained small.

In conclusions, in VM patients, RNFL thinning is positively correlated with WMLs, which suggests an underlying common ischemic pathophysiology. However, RNFL thickness did not correlate significantly with visual aura symptoms, indicating that the mechanism of visual aura symptoms is not vascular in nature. The specific mechanism of VM still needs to be further explored.

DISCLOSURE

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Conflict of interest: None

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