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Preliminary study of the role of inner ear proteins in vestibular neuritis

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ABSTRACT

Objective: To evaluate the plasma levels of the otoconial proteins, otoconin-90 and otolin-1, in individuals diagnosed with vestibular neuritis (VN) and determine the feasibility of using these proteins as biomarkers for VN.

Methods: In this preliminary study, 30 patients diagnosed with VN and 70 healthy individuals were recruited and followed to confirm whether they had benign paroxysmal positional vertigo (BPPV) during the following time. The recorded data included measurements of height, weight, and history of diabetes mellitus or hypertension. Additionally, levels of plasma otoconin-90, and otolin-1 were measured and compared.

Results: The plasma concentrations of otoconin-90 and otolin-1 may not be significantly different between patients with VN and healthy controls, nor among patients with BPPV secondary to VN and patients with VN without BPPV.

Conclusions: Plasma otoconin-90 and otolin-1 levels may not serve as biomarkers of acute VN episodes or predict BPPV occurrence secondary to VN.

1. Introduction

Vestibular neuritis (VN) manifests as unprovoked dizziness due to unilateral malfunction of the vestibular system. The main manifestations of VN are sudden, persistent vertigo, nausea, vomiting, spontaneous horizontal rotatory nystagmus beating towards the unaffected side, and balance dysfunction, without hearing changes or central nervous system injury (Le et al., 2019; Strupp and Magnusson, 2015). VN is primarily diagnosed based on clinical manifestations, signs, and vestibular function tests (Nandar Kurniawan and Kaysa Waafi, 2021; Professional Committee on Vertigo, 2020). It is difficult to cooperate with these relevant examinations when a patient is in an acute attack episode. Consequently, it holds significant importance to delve into the diagnostic indicators of VN.

Otoconin-90 is the most common otoconial protein, accounting for 90 %, otolin-1 5 %, and the remaining 5 % (Mulry and Parham, 2020; Huang and Qian, 2022). Recent researches have confirmed that otolin-1 and otoconin-90 are measurable in the peripheral blood, functioning as biomarkers in discerning inner ear diseases, such as benign paroxysmal positional vertigo (BPPV) (Bi et al., 2021; Parham et al., 2014; Avallone et al., 2022; Feng et al., 2019; Guerra and Devesa, 2020; Tabtabai et al., 2017). So far, only one study has explored the differences in blood otolin-1 levels among patients with VN and healthy individuals (Avallone et al., 2022). Nevertheless, there was no discernible disparity observed between the two groups. The objective of this research was to analyze the plasma concentrations of otoconin-90 and otolin-1 between patients with VN and healthy controls and evaluate their role in the pathogenesis and clinical diagnosis of VN.

2. Materials and methods

2.1. Subjects

Between June 2021 and December 2022, 30 individuals diagnosed with VN and 70 asymptomatic controls, who had no prior experience of vertigo or dizziness were chosen from the Ningbo No. 2 hospital. The diagnosis of VN relied on the Multidisciplinary Experts Consensus on Vestibular Neuritis in China (Professional Committee on Vertigo, 2020):

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1) acute, first, and persistent vertigo, with nausea, vomiting, and postural instability; 2) no hearing loss or other focal neurological symptoms and/or signs; 3) spontaneous nystagmus with slight torsion at the unidirectional level and positive head shake test on the affected side; and 4) unilateral vestibular nerve function weakening. The rule-out criteria were as follows: 1) history of BPPV, Meniere's disease (MD), migraine, head trauma, inner ear surgery, otitis media, or labyrinthitis; 2) acute or chronic infection; 3) chronic liver and kidney failure; 4) hormone treatment before blood collection; and 5) uncooperative participants.

The Ethics Committee of Ningbo No. 2 Hospital has granted approval for this study. (protocol number KY-2020-038). Further, each participant provided informed consent before the experiment.

2.2. Data collection

Baseline information including age, height, weight, personal history, and past diseases was collected. Once the VN diagnosis was confirmed, patients received symptomatic treatment, causal treatment, and physical rehabilitation. All patients were discharged after their symptoms improved and followed-up by telephone interview or out-patient at 3, 6, 12, and 24 months to confirm the presence of BPPV. The diagnosis of BPPV was based on clinical history and characteristic nystagmus during positional testing, according to the US clinical practice guideline for BPPV (Bhattacharyya et al., 2017). If the patient is followed up by telephone, medical experiences and typical symptoms, such as temporary vertigo induced by a rapid change in head position, were asked.

2.3. Biochemical analysis

Morning blood samples obtained after fasting were collected from all participants and subsequently underwent centrifugation at a speed of 3000 rpm for 10 min. The resulting plasma was stored at −80 °C until the assay was conducted. Otoconin-90 and otolin-1 levels in the plasma were quantified utilizing Human otoconin-90 and otolin-1 enzyme-linked immunosorbent assay kits (QAYEEBIO, Shanghai, China), following the instructions provided by the manufacturer.

2.4. Statistical analysis

Statistical analyses were conducted employing SPSS (version 26.0; Chicago, IL, USA). Distribution normality was using the mean ± SD; otherwise, they were expressed by median (quartile). Descriptions for qualitative variables include numerical values and percentages. The normality distribution was examined using the Shapiro–Wilk test. When data followed a normal distribution, group comparisons were performed using an independent-sample *t*-test. Conversely, the Mann-Whitney *U* test is a statistical analysis technique used for comparing independent samples when the data is not normally distributed. The level of significance was determined to be a *p*-value of 0.05.

3. Results

3.1. Demographics of the subjects

In this research, 30 individuals diagnosed with VN and 70 healthy individuals were enrolled. The median ages of the VN and controls were 55 and 60 years, respectively. The interval between the onset of symptoms and collection of a blood sample varied from 0.20 day to 45 days (mean = 5.47 days, median = 3.00 days), and 90% of the patients were evaluated within a week from symptom onset. The attributes of the study population are age, BMI, percentage of patients with hypertension and diabetes mellitus, as well as smoking and alcohol consumption, as seen in Table 1.

Table 1
Clinical characteristics of patients with VN and controls.

Characteristics	VN (n = 30)	Healthy controls (n = 70)	*P-value*
Sex (F/M)	14/16	39/31	0.599
Age (year)	55.00 (48.25, 66.00)	60.00 (53.75, 67.00)	0.084
BMI (kg/cm2)	23.17 ± 2.80	24.07 ± 2.95	0.266
Hypertension [n (%)]	13 (43.30%)	38 (54.29%)	0.315
Diabetes [n (%)]	3 (10.00%)	6 (8.57%)	1.000
Smoking [n (%)]	5 (16.70%)	19 (27.10%)	0.246
Drinking [n (%)]	4 (13.30%)	15 (21.43%)	0.329
Otoconin-90 (ng/mL)	27.84 (26.84, 42.05)	29.37 (27.27, 32.01)	0.922
Otolin-1 (pg/mL)	135.69 (116.06, 222.10)	137.25 (111.23, 152.77)	0.093

VN, vestibular neuritis; BMI, body mass index was defined as the quotient of an individual's weight in kilograms divided by the square of their height in meters. P-values <0.05 were considered significant.

3.2. Comparison of otoconin-90 and otolin-1 between patients with VN and healthy controls

Figs. 1 and 2 show the distribution of plasma otoconin-90 and otolin-1 concentrations in the two groups. The median concentration of otoconin-90 was 27.84 ng/mL and 29.37 ng/mL for the two groups, and otolin-1 was 135.69 pg/mL and 137.25 pg/mL for the patients with VN and controls, respectively. Plasma concentrations of otoconin-90 and otolin-1 did not exhibit any statistical differences between the two groups ($p = 0.922, 0.093$, $p > 0.05$; Table 1).

3.3. Comparison of otoconin-90 and otolin-1 levels between patients with BPPV secondary to VN and patients with VN without BPPV occurrence

There were five cases of loss, two cases of recurrent VN, and 6 (24 %) patients with VN who experienced BPPV during the follow-up period. Among them, three patients were based on in-person assessments, and the other three were diagnosed with BPPV in other hospitals during telephone follow-up. The longest time from the onset of VN until the manifestation of BPPV was 17 months, and none of them had a history of vascular or trauma. Plasma otoconin-90 and otolin-1 levels showed no significant variation between patients with VN with and without

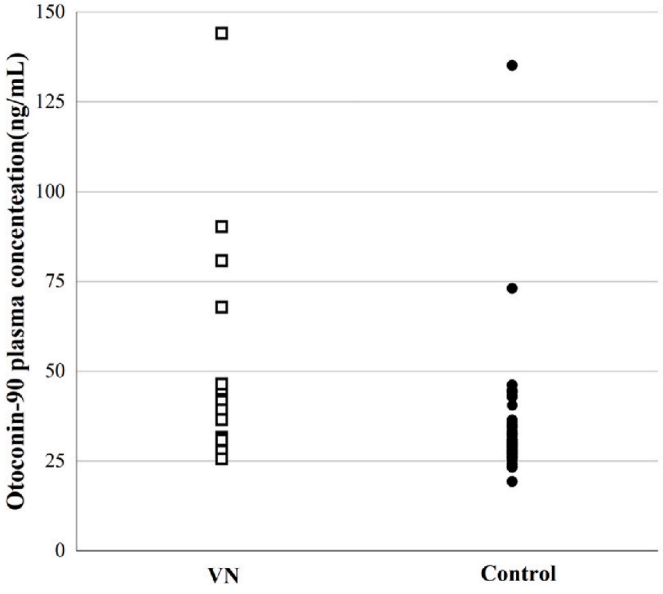

Fig. 1. Plasma otoconin-90 concentration in patients with VN and controls.

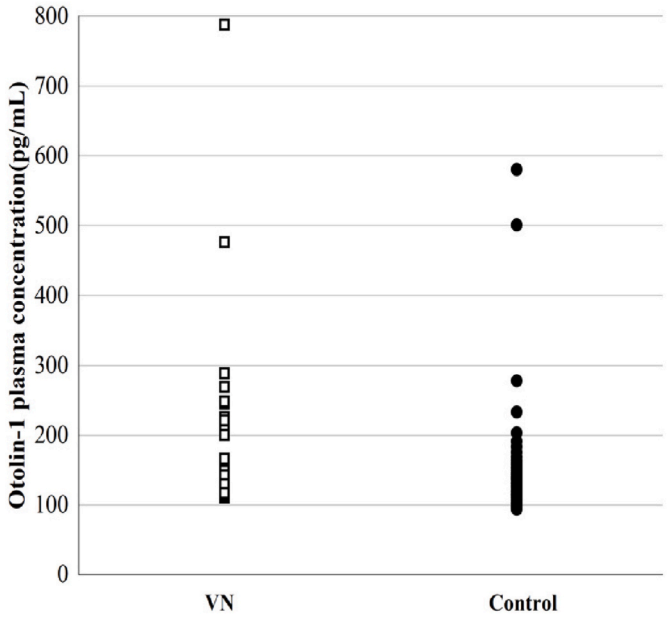

Fig. 2. Plasma otolin-1 concentration in patients with VN and controls.

secondary BPPV ($p > 0.05$); see Table 2.

4. Discussion

Given the specificity of otoconin-90 and otolin-1 and their important roles as biomarkers for inner ear disease, this study explored the relationship between otoconin-90, otolin-1, and VN. Our study showed that the plasma concentrations of otoconin-90 and otolin-1 of individuals diagnosed with VN exhibited no notable disparities when contrasted with the controls. Moreover, there was also no notable difference among those with or without secondary BPPV occurrence in patients with VN.

Through a small sample study, Parham et al. (2014) initially observed that the plasma concentrations of otolin-1 in individuals affected by BPPV were heightened compared to the control group. Since then, inner ear proteins have been extensively studied. Studies have denoted that the blood concentrations of otolin-1 in individuals with MD and sudden hearing loss and in patients who underwent mastoidectomy, and the serum concentrations of otoconin-90 in patients affected by BPPV were significantly higher compared to the controls (Murat D et al., 2019; Wu, Y et al., 2020; Bi et al., 2021; Avallone et al., 2022). These reports suggest that serum concentrations of otoconin-90 and otolin-1 could potentially be used as biomarkers for inner ear disorders.

VN is a primary instigator of vertigo (Mandalà et al., 2023), and its characteristic manifestations include a sudden occurrence of vertigo, nausea, and/or vomiting, without hearing changes and neurological signs. To date, one pilot study recruited 18 patients with VN to investigate the potential of otolin-1 as a serological indicator for VN (Avallone et al., 2022). In contrast to previous studies, we found that there is no notable disparity in the serum levels of otolin-1 between VN and controls. In this study, we expanded the sample size and added a new biomarker, otoconin-90. Similarly, the plasma concentrations of otolin-1 and otoconin-90 exhibited no discernible variance between VN and controls.

Table 2
Comparison of otoconin-90 and otolin-1 between patients with BPPV secondary to VN and patients with VN without BPPV occurrence.

	BPPV secondary to VN (n = 6)	No BPPV secondary to VN (n = 17)	*P-value*
Otoconin-90 (ng/mL)	29.32 (26.57,103.68)	27.44 (26.72,36.46)	0.575
Otolin-1 (pg/mL)	179.55 (116.56,544.16)	119.77 (115.84,188.39)	0.263

VN, vestibular neuritis; BPPV, benign paroxysmal positional vertigo.

BPPV secondary to VN has been studied with a range of approximately 9.8–31.6 % (Balatsouras et al., 2014; Türk et al., 2021). Although the etiology of BPPV secondary to VN is unknown, there are two hypotheses. First, the cause of VN may be the reactivation of a latent herpes simplex virus type 1 in the vestibular nerve ganglion, which often affects the superior vestibular nerve (Gianoli et al., 2005). The superior vestibular nerve receives nerve fiber from the anterior semicircular canal, horizontal semicircular canal and utricle. Therefore, VN can cause semicircular canal dysfunction and otolith membrane degeneration. Another possible pathogenetic mechanism is ischemic distress related to the anterior vestibular artery (Hemenway and Lindsay, 1956). If it is labyrinthine ischemia, it may lead to otoconial degeneration (Kim et al., 2023). Both of these hypotheses can cause the otolithic debris moves to new positions, which can cause BPPV. Consequently, inner ear proteins can exit the endolymph, pass through the labyrinth-blood barrier, and enter the systemic circulation.

In this preliminary investigation, we explored the potential value of otoconin-90 and otolin-1 as biomarkers for predicting secondary BPPV after VN. During the follow-up period, 24 % (6/25) of patients with VN experienced BPPV occurrence. There was no discernible discrepancy in concentrations of otolin-1 and otoconin-90 between patients with and without secondary BPPV after VN, heralded that these biomarkers may have no predictive value for BPPV after VN.

Our research encountered certain limitations. Firstly, it was a single-center study with a limited cohort size. Therefore, it is impossible to draw a definite conclusion about the otolith protein of BPPV secondary to VN. Additionally, the causative relation of the two conditions could not be proven in our study. Secondly, the follow-up duration of each patient with VN was different, ranging from six months to two years. Some patients with VN may later develop secondary BPPV. Finally, we did not measure otoconial proteins levels in secondary BPPV. In the future, we will expand the sample size to determine the critical values of plasma otolin-1 and otoconin-90 to further guide the clinical diagnosis of VN.

5. Conclusion

Otoconin-90 and otolin-1 can be quantitatively measured in peripheral blood; however, they might not serve as biomarkers for acute VN episodes or predict BPPV secondary to VN.

Ethics approval and consent to participate

The study was approved by the Ningbo No.2 Hospital (protocol number KY -2020-038) and performed according to the principles of the Declaration of Helsinki. All participants provided written informed consent before enrollment.

Consent for publication

We have obtained written consent from all patients to publish this paper.

Availability of data and materials

Please kindly direct any inquiries regarding the supporting data for the findings of this article to the following email address: wu_yunqin@126.com for access.

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Declaration of competing interest

All authors have no potential conflicts of interest to be disclosed.

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