The Investigation of Salivary Calcitonin-Gene Related Peptide (CGRP) in Vestibular Migraine

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Background

• Migraine is a prevalent neurologic disorder. Vertigo occurs in as commonly as 25% of migraine patients.[1]
• *Vestibular migraine* (VM) was established as a distinct diagnosis in the 2014 edition of International Classification of Headache Disorders (ICHD) (Figure 1).[2] The underlying etiologies of VM are not well understood.
• Within the last decade, epidemiologic studies have linked recurrent vestibular symptoms with features of classic migraine.[3]
• Classic migraine and VM may therefore share a common pathophysiologic origin.

Figure 1: The diagnostic criteria of VM, from a consensus statement of the International Headache Society and Bárány Society of Neuro-Otology.[3]

1. *At least 5 episodes with vestibular symptoms of moderate or severe intensity, lasting 5 minutes to 72 hours;*
2. *Current or previous history of migraine with or without aura according to the 2004 criteria of the International Headache Society;*
3. *One or more migraine features with ≥50% of the vestibular episodes. These features include:*
   - *i. Headache with at least 2 of the following characteristics: unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by routine physical activity;*
   - *ii. Photophobia or phonophobia;*
   - *iii. Visual aura;*
4. *Not better accounted for by another vestibular or International Classification of Headache Disorders diagnosis.*

• CGRP is a vasoactive neuropeptide released from the trigeminal efferent pathways. It has been implicated in the *trigeminovascular hypothesis* of migraine pathogenesis.[4-6]
• The heterogeneous presentation and poorly understood etiology rendered VM a diagnostic challenge. Currently, there are no biologic markers for VM.

Outcome Objectives

In the present study, we plan to:

Aim 1: Determine if salivary CGRP level changes with physiologic vertigo induced by caloric testing in controls;
Aim 2: Determine whether CGRP level differs in patients with VM and migraine compared to controls;
Aim 3: Assess whether salivary CGRP level changes are correlated with migraine and VM severity.

Methods

Participants:
• Controls: no migraine or dizziness/vestibular complaints; underwent caloric stimulation to induce physiologic vertigo.
• Migraine: physician diagnosis of migraine and met the 2014 ICHD criteria for migraine.
• Vestibular migraine: physician diagnosis of VM and met the 2014 ICHD criteria for VM.
Setting: Neuro-otology clinic, migraine clinic, 11/15-05/16
Sample collection:
• 3mL un-stimulated whole saliva samples
• Controls provide a sample before and after the caloric test.
Analysis:
• CGRP enzyme-linked immunoassays (Cayman Chemical, MI)
• ANOVA to compare mean CGRP levels; multivariable linear regression to evaluate the association between symptom severity and CGRP levels.

Results

Table 1: Demographics and symptoms of the study cohort

Study variables	Controls (n=21)	Migraine (n=22)	VM (n=21)	*p-value*
Age in years (SD)	30.9 (10.9)	41.6 (14.1)	45.8 (13.2)	**<0.01**
Sex (n, %):				
Male	10 (47.6)	5 (22.7)	5 (23.8)	0.15
Female	11 (52.4)	17 (77.3)	16 (76.2)	
Race/ethnicity (n, %):				
White	10 (47.6)	17 (77.3)	18 (85.7)	
African American	1 (4.8)	3 (13.6)	1 (4.8)	**<0.01**
Other	10 (47.6)	2 (9.1)	2 (9.5)	
Disease category (n, %)				
Inactive		4 (18.2)	8 (38.1)	
Interictal	--	11 (50.0)	8 (38.1)	0.23
Active		7 (31.8)	5 (23.8)	
Symptoms during the most recent episode				
Vertigo (n, %)	--	8 (36.4)	21 (100)	**<0.01**
Headache (n, %)	--	22(100)	9 (42.9)	**<0.01**
Ear pain (n, %)	--	3 (13.6)	3 (14.3)	0.21
Ear pressure (n, %)	--	5 (22.7)	11 (52.4)	**<0.01**
Hearing loss (n, %)	--	0	1 (4.8)	0.37
Tinnitus (n, %)	--	5 (22.7)	11 (52.4)	**<0.01**
Fall (n, %)	--	1 (4.5)	2 (9.5)	0.53
Photophobia (n, %)	--	21 (95.5)	12 (57.1)	**<0.01**
Phonophobia (n, %)	--	16 (72.7)	11 (52.4)	0.18
Diplopia (n, %)	--	1 (4.5)	2 (9.5)	0.53
Nausea/vomiting (n, %)	--	11 (50.0)	13 (61.9)	**<0.01**

Table 2: Salivary CGRP (pg/mL) by disease category

Type of participants	Inactive/Pre-caloric test	Interictal	Active/Post-caloric test	*p-value*
Controls (SD)	10.4 (13.1)	--	14.5 (17.2)	0.45
Migraineurs (SD)	42.9 (29.1)	56.0 (59.3)	75.9 (64.8)	0.63
Vestibular migraine pts (SD)	16.6 (16.3)	122.1 (116.1)	91.9 (53.0)	**0.04**

Figure 2: (Left) mean salivary CGRP level before and after caloric testing in controls; (right) salivary CGRP levels differ among controls, migraine patients, and VM patients.
Note: *Error bar represents the standard error

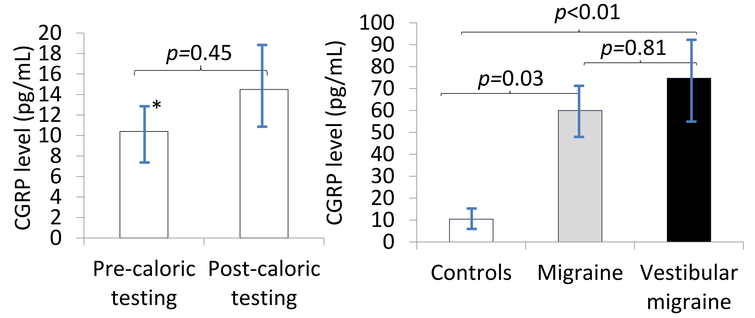
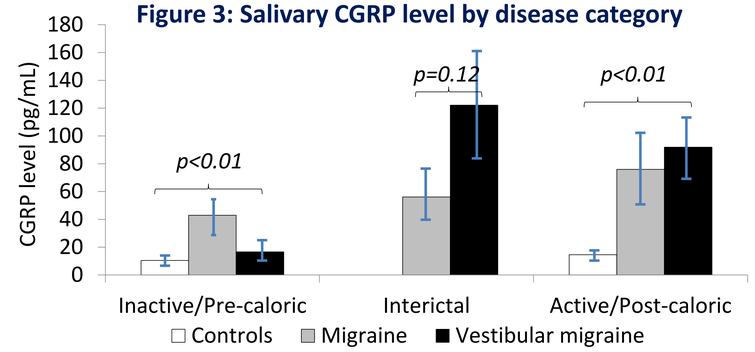


Figure 3: Salivary CGRP level by disease category



• In multivariate linear regression analysis adjusting for age, sex, and race, none of the symptoms is significantly associated with salivary CGRP level.

Conclusion

• Salivary CGRP levels are elevated in patients with VM just as in those with migraine headache.
• Controls with physiologic vertigo do not show elevated salivary CGRP levels.
• Findings suggest that trigeminovascular inflammation, which plays a role in migraine pathophysiology, may also be relevant to VM and not just a nonspecific response to vertigo.
• Further research is needed to assess temporal changes of CGRP during different migraine disease states, define the role of inflammatory neuropeptides as biomarkers for VM, and explore if labyrinthine inflammation mediated by peptides could be a treatable target of vertigo in VM.

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