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Original Research Article

A Cross-Sectional Analytical Study of Retinal Microvascular Changes in Migraine Patients in a Tertiary Care Center

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Abstract:

Background: Migraine is a complex neurological disorder characterized by recurring headache, with distinct phases. Neurovascular dysfunction and hypothalamic activation are pathophysiological mechanisms of migraine. Cerebral microvascular damage has been implicated in migraine. As cerebral and retinal microvasculature share similar embryology, anatomy and physiology, changes in retinal microvasculature may mirror changes in cerebral microvasculature. This study was aimed to look into the retinal microvascular abnormalities in migraine patients.

Objective: This study aims to look into the relationship between migraine and retinal microvascular abnormalities and to compare the results between groups of migraine with aura, migraine without aura, and non-migraine headaches

Methods: This cross-sectional analytical study included 312 patients with primary headaches after ruling out secondary causes at Tirunelveli Medical College Hospital (TVMCH) between August 2021 and December 2022. A semi structured interview was done with each participant to gather clinical information about their headache characteristics using ICHD 3 criteria and classified headache patients in to migraine with aura, migraine without aura and non-migraine headaches groups. Retinal microvascular abnormalities were evaluated using fundus photographs from an indirect ophthalmoscope. Retinal microvascular abnormalities recorded includes retinopathy, focal arteriolar narrowing, and arteriovenous nicking.

Results: Of the 312 patients, 82 presented had migraine with aura, 118 had migraine without aura, and 112 had non migraine headache. Female patients were affected in both migraine groups. Retinopathy was observed in 52 patients of migraine with aura group, 12 patients of migraine without aura group, and 8 patients of non-migraine headache group. Focal arterial narrowing was noted in 68 patients of migraine with aura, 16 patients of migraine without aura, and 10 patients of non-migraine headache. Focal arteriolar narrowing and arteriovenous nicking were more in patients of migraine with aura. Statistical analysis revealed a significant association between migraine aura and retinal abnormalities ($p = 0.0027$).

Conclusion: Migraine is associated with retinal microvascular abnormalities, including retinopathy, focal arteriolar narrowing, and arteriovenous nicking. Migraine with aura is more associated with retinal microvascular abnormalities compared to migraine without aura and non-migraine headaches.

Keywords: Migraine, Retinopathy, Retinal Microcirculation, Aura, Focal Arteriolar Narrowing, Arteriovenous Nicking.

Introduction

Migraine, a prevalent form of primary headache, is a significant contributor to disability, imposing a substantial impact on society and families. [1] The evaluation for migraine are outlined by the International Classification of Headache Disorders (ICHD). [2] Migraine episodes typically progress from a distinct phases: prodrome, aura, headache, and postdrome, each characterized by a wide range of complex symptoms and neurological disturbances. [3] Aura, which precedes the headache in approximately one-third of patients and can last from several hours to days, manifests as visual, sensory, language, or brainstem dysfunctions. [4] The phenomenon of cortical spreading depression (CSD) observed to be impacting and contributing to the aura stage. [5] CSD is characterized by alterations in cortical potentials and dynamic blood flow changes. [1] This process involves an influx of water, calcium and sodium, including the efflux of ATP, protons, potassium, protons, and glutamate passing through the cells and interacting with adjacent cells

followed by activation of meningeal nociceptors and the perivascular trigeminal nerve. [6]
A different theory for the development of migraines, especially those without an aura, suggests the hypothalamus as a key contributor. In this framework, factors like stress, sleep disruption, and mood fluctuations stimulate the hypothalamus, which subsequently sends parasympathetic signals to the superior salivary nucleus (SSN). Connection of SSN to the meninges via postganglionic parasympathetic neurons in the sphenopalatine ganglion (SPG), leads to the activation of meningeal nociceptors and the involvement of trigeminal vascular pathways. [7] The trigeminal vascular system consists of a complex web of pain-sensitive fibers from the trigeminal ganglion that supply various intracranial structures, including the leptomeninges, arachnoid, dural vessels, and cerebral arteries. When activated by cortical spreading depression (CSD) or hypothalamic signals, these fibers release neuropeptides such as calcitonin gene-related peptide and substance P, causing vasodilation in the dura mater and leptomeninges and triggering the release of pro-inflammatory cytokines. [8]

Nociceptive signals also pass via afferent fibers to the peripheral trigeminal ganglia and synapse on neurons in the trigeminal cervical complex (TCC). Signals from the TCC then go to several brain areas, including the hypothalamus, brainstem, thalamus, and basal ganglia. Cortical regions involved in processing these inputs lead to the appearance of migraine symptoms and related phenotypic features. [9] A increasing corpus of evidence suggests a link between migraine and vascular disease. Migraine with aura has been identified as an independent risk factor for recurrent vascular events, including ischemic stroke, particularly in younger people with a history of ischemic stroke. [10]

Furthermore, migraine patients appear to be at a higher risk of transient ischemic attacks (TIA). [11] Recent population-based cohort studies have found that migraine aura is associated with an increased risk of death from coronary artery disease. [12]

Furthermore, studies have found a link between migraine and vascular-related mortality [13], as well as vascular diseases in the lower limbs and eyes [14], including Raynaud's syndrome, retinal artery blockage, and glaucoma. This link might be due to a vascular susceptibility unique to migraine sufferers, which not only contributes to migraine onset but also raises the risk of developing other vascular disorders over time. [15]

Additionally, migraine has been identified as a risk factor for coronary artery disease. [17] Biomarkers indicative of large vessel diseases, such as atherosclerosis, have been linked to cerebrovascular conditions [19] and have been thoroughly investigated in relation to migraine. [20] However, the shared mechanisms between these conditions remain unclear. Emerging evidence points to the role of microvascular pathology in the development of stroke and coronary artery disease. [21] Likewise, microvascular damage has been associated with migraine, providing valuable clues to its underlying mechanisms.

Aim

The purpose of this study was to look into the relationship between migraine and retinal microvascular abnormalities and to compare the results between groups of migraine with aura, migraine without aura, and non-migraine headaches.

Materials and Methods

This cross-sectional analysis included 312 patients who were diagnosed with primary headache in the Department of Neurology at Tirunelveli Medical College Hospital (TVMCH) between August 2021 and December 2022. The study was conducted with prior clearance from the Institutional Ethics Committee, and all subjects provided informed consent.

Inclusion criteria

This study comprised patients aged 18 to 50 years who had been diagnosed with primary headache. They are classified in to migraine with aura, migraine without aura and non-migraine headaches according to the ICHD-3 criteria and had given their consent to participate.

Exclusion criteria

This study excluded patients with a history of diabetes, hypertension, smoking, alcohol consumption, cardiovascular disease, or cerebrovascular disease, as well as those with other secondary causes of headaches such as sinusitis, space-occupying lesions (SOL), or neoplasms, and primary ocular disorders such as glaucoma.

Methodology

A semi Structured interview was done with each participant to gather clinical information about their headache characteristics using ICHD 3 criteria by asking following history.

At least 5 headache attacks lasting at least 4 hours 2) headache unilateral location, pulsating quality, moderate to severe intensity, aggravation by routine physical activity 3) headache associated with nausea, vomiting, or sensitivity to light or sound.

Additionally, history of aura lasting at least 5 minutes (including one or more of visual, sensory,

language, motor, brainstem, retinal aura) was included to differentiate migraine with aura from migraine without aura. Headaches not satisfying migraine criteria referred to as non-migraine headaches.

Fundus pictures were taken with an indirect ophthalmoscope to assess each patient's retinal condition. Retinal microvascular abnormalities such as retinopathy, localized arteriolar constriction, arteriovenous nicking, and arteriolar and venular caliber were assessed. Retinopathy was defined based on the presence of at least one of the following lesions: retinal hemorrhages (blot or flame shaped), microaneurysms, soft or hard exudates, macular edema, venous beading. Retinal arteriolar and venular calibres were estimated utilizing a semi-automatic technique to interpret fundus changes, allowing for objective assessment of retinal vascular diameter.

Statistical analysis

Data was gathered, entered, and validated on a Microsoft Excel spreadsheet. Data was analyzed using SPSS version 23.0. The study's findings were summarized using descriptive statistics, with the proportion of migraine patients with, without aura, non-migraine headaches were given as a percentage. Similarly, the percentage of migraine patients with retinopathy or other retinal microcirculation anomalies was determined. Retinal abnormalities were classified and the results were provided in statistical tables.

Results

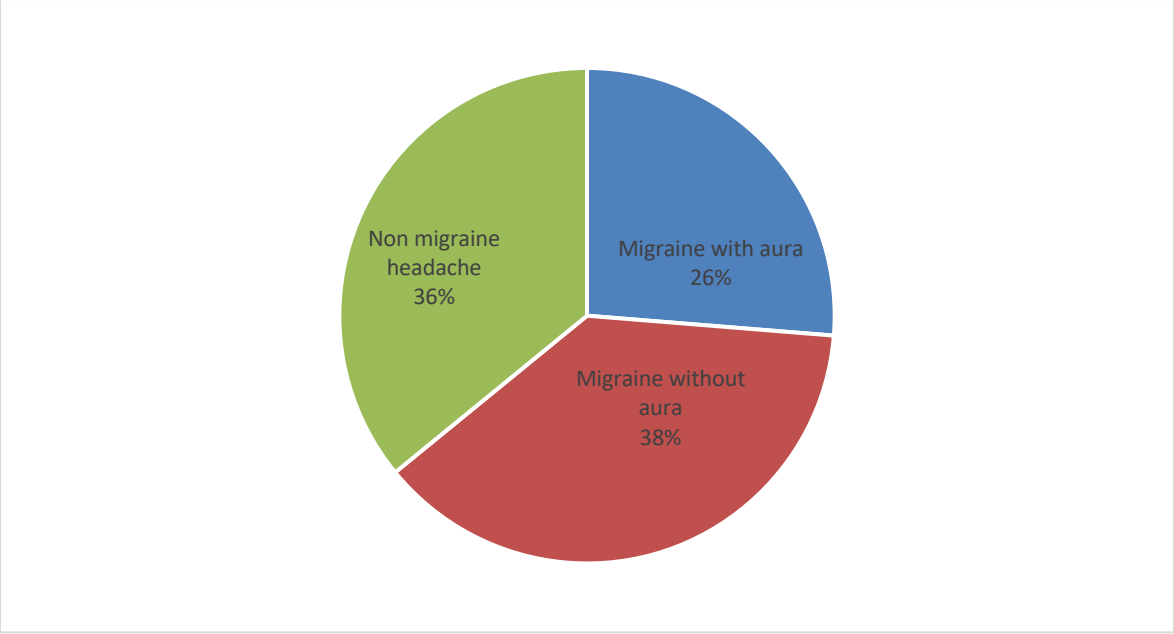

Figure 1: Headache distribution

In this study 26% of patients presented with migraine with aura, 38% patients presented with migraine without aura, and 36% of the patients presented with non-migraine headache (Figure 1).

Table 1: Comparison gender-wise in patients

		Migraine with aura	Migraine without aura	Non migraine headache
Gender	Women	58	80	68
	Men	24	38	44

The migraine with aura group (n=82) had 58 females and 24 males. Migraine without aura group (n = 118) had 80 females and 38 males. Non-migraine headache group (n=112) had 68 females and 44 males.(Table 1).

Table 2: Retinal microvascular abnormalities in different groups

		Migraine with aura	Migraine without aura	Non migraine headache	P value
Condition	Retinopathy	52	12	8	0.0027
	Focal Arteriolar Narrowing	68	16	10	
	Arterio-Venous Nicking	42	26	14	

In a group of migraine with aura (82 patients), 52 patients had retinopathy, 68 patients had focal arteriolar narrowing and 42 patients had arteriovenous nicking. In contrast, in a group of migraine without aura (118 patients) displayed with 12 patients of retinopathy, 16 patients of focal arteriolar narrowing, and 26 patients of arteriovenous nicking. In group of non-migraine headache (n = 112) 8 patients had retinopathy, 10 patients had focal arteriolar narrowing, and 14 patients had arteriovenous nicking.

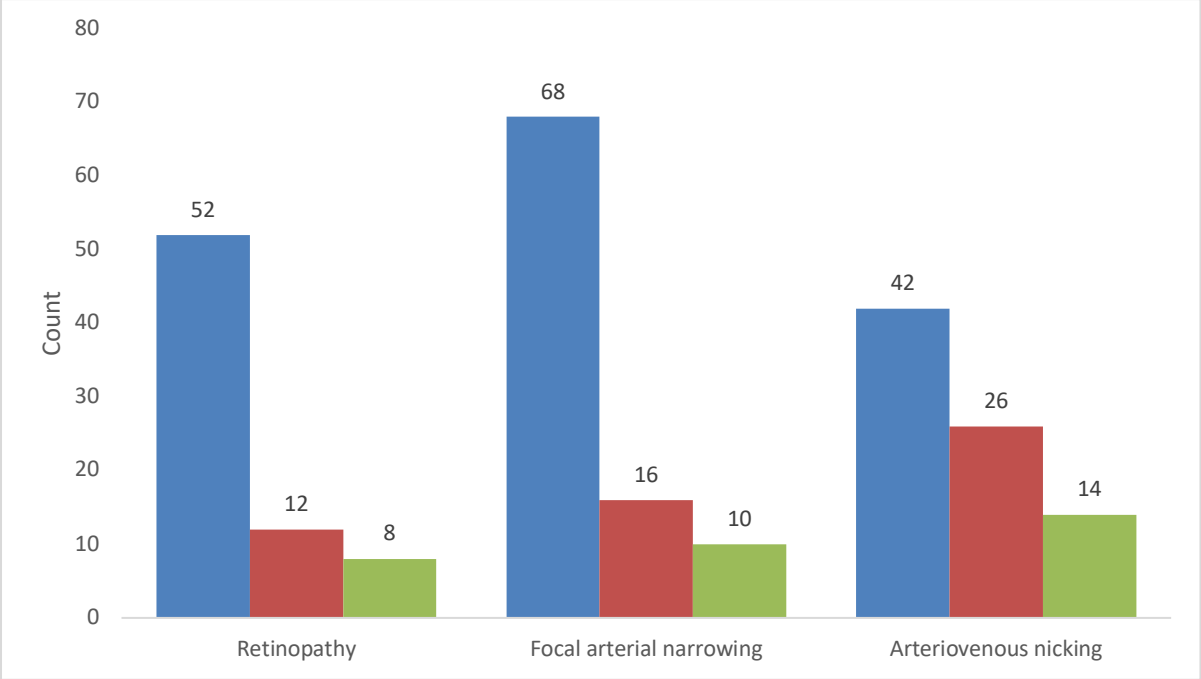

Figure 3: Comparison of Retinal microvascular abnormalities in different groups

Retinopathy was found in 52 patients of migraine with aura, 12 patients of migraine without aura, and 8 patients of non-migraine headache. Focal arteriolar constriction was seen in 68 patients of migraine with aura, 16 patients of migraine without aura, and 10 patients of non-migraine headache patients. Arteriovenous nicking was seen in 42 patients of migraine with aura, 26 patients of migraine without aura, and 14 patients of non-migraine headache patients. Retinopathy was predominantly found in migraine with aura group compared with other groups. Focal arteriolar constriction was more observed in migraine with aura group compared with other groups. Arteriovenous nicking predominantly found in migraine with aura group compared with other groups, with p=0.0027 indicating statistical significance.

Discussion

The results of this study reveal significant differences in headache types and associated retinal microvascular abnormalities among patients. Notably, a striking distribution of headache types was observed: 26% of patients experienced migraines with aura, 38% reported migraines without aura, and 36% suffered from non-migraine headaches.

This highlights the prevalence of migraine disorders in the patient population, particularly the substantial proportion of those with migraines without aura.

Gender Distribution

The gender analysis in Table 1 demonstrates a clear predominance of females in both migraine categories, with women constituting 70.7% of the migraine with aura group and 67.8% of the migraine without aura group.

This aligns with existing literature, which consistently shows that migraines are more common in females than males, likely due to hormonal influences. Interestingly, while the non-migraine headache group also had more females, the gender distribution was less skewed compared to the migraine groups, suggesting that non-migraine headaches may not be as closely linked to gender-specific factors.

Retinal Microvascular Abnormalities

Table 2 and Figure 3 illustrate the presence of retinal microvascular abnormalities, particularly highlighting the pronounced differences in the migraine with aura group. The high prevalence of retinopathy (63.4%) in patients with migraines with aura stands in stark contrast to the lower rates observed in the other groups (10.2% in migraine

without aura and 7.1% in non-migraine headaches). The presence of focal arteriolar narrowing and arteriovenous nicking further emphasizes the vascular implications associated with migraines with aura.

The significant P-value of 0.0027 indicates a strong statistical relationship between migraines with aura and the presence of these retinal abnormalities. This suggests that the underlying pathophysiological mechanisms of migraine with aura may involve more pronounced vascular changes, potentially linking migraine to broader cardiovascular risks. These findings support the hypothesis that migraines with aura could serve as an indicator of vascular health issues, warranting further investigation into long-term outcomes for this patient population.

Clinical Implications

The data underscore the importance of thorough ophthalmologic assessments in patients presenting with migraines, particularly those with aura. Given the association with retinal abnormalities, healthcare providers may need to adopt a more proactive approach to monitor and manage vascular health in these patients. Recognizing the potential link between migraines with aura and vascular disease could aid in early intervention strategies aimed at reducing future vascular events.

Limitations and Future Directions

While the study provides valuable insights, it is important to acknowledge its limitations, including relatively small sample size may have constrained the generalizability of the findings and diminished the statistical power to detect certain associations and the cross-sectional design which restricts causal inferences. Classification of migraine status relied on patients' recollection of their headache symptoms, introducing the potential for recall bias, which could compromise the accuracy of the data.

Conclusion

This study reinforces the association between migraine with aura and significant retinal microvascular abnormalities, highlighting the necessity for increased awareness of the vascular implications of migraine disorders.

These findings not only contribute to the existing literature on migraines but also pave the way for future research aimed at improving patient care and outcomes in this population.

The present study demonstrated that migraine patients exhibit a higher prevalence of retinal microvascular abnormalities compared to individuals without headaches. Patients experiencing migraine with aura are more likely to present with these abnormalities than those experiencing migraine without aura.

The observed alterations in the retinal microvasculature may serve as potential biomarkers, reflecting similar changes occurring in the cerebral microvasculature. This underscores the importance of further investigation into the retinal-cerebral vascular connection in patients with migraine.

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