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Original Research Article

Compare Pupil Size in Migraine Patients with Photophobia versus Normal Subjects and Correlation of the Pupil Size to Severity of Headache

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Abstract:

This study suggests that patients with migraines and photophobia have significantly larger pupil sizes compared to normal subjects without headaches. The findings indicate a correlation between pupil size and the severity of migraine disability as measured by the Migraine Disability Assessment (MIDAS) test. Migraine patients with photophobia had a mean pupil size of 4.89 mm, while normal subjects had a mean of 3.8 mm. The difference was statistically significant. Based on MIDAS grades, patients with more severe disability (Grade 4) had the largest pupil size, averaging 5.6 mm. This indicates a potential link between larger pupil size and greater migraine severity. The study concludes that larger pupil size could potentially trigger migraine attacks, and the severity of migraine symptoms increases as pupil size increases.

Keywords: Migraine with photophobia, pupil and Migraine Disability Assessment (MIDAS) test.

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Introduction

Migraine is a highly prevalent condition, being the third most common disease globally, affecting approximately 14.7% of the population (one in seven people). [1] Photophobia, or light sensitivity, is a key symptom in 80% of migraine cases, making it a central component of the disorder. For about one-third of migraine patients, exposure to bright light serves as a trigger for their migraine attacks. This emphasizes the strong link between migraine, photophobia, and external light stimuli as a trigger for attacks. Understanding this relationship can help in managing and possibly reducing the frequency of migraine episodes through light control and other interventions. [2]

The diagnosis of migraines is typically based on clinical criteria, which include symptoms like unilateral, throbbing pain that worsens with physical activity and is often accompanied by nausea and heightened sensitivity to light (photophobia) and sound (phonophobia). [3] Among these features, photophobia is particularly common and disabling, making it a key diagnostic criterion. Photophobia, in the context of migraines, refers to the triggering or worsening of headache symptoms due to exposure to light. Notably, many individuals with migraines experience light sensitivity even between attacks, a phenomenon supported by evidence showing lower interictal (between migraine episodes) light sensitivity thresholds in migraine patients compared to those without headaches.[4] This suggests that migraines have an ongoing heightened sensitivity to light even outside of acute migraine attacks. The exact mechanism behind photophobia in migraines remains unclear, but several neural circuits have been proposed to explain the phenomenon: The brain, particularly the cortex, may become overly sensitive to light stimuli during a migraine, leading to exaggerated responses to normal light exposure. [5] Changes in the parasympathetic nervous system's control over the eye could contribute to the abnormal light sensitivity, potentially affecting how the eyes and brain respond to light during a migraine attack. These specialized cells in the retina respond directly to light and influence neurons in the thalamus that are sensitive to pain from the dura mater (the membrane surrounding the brain).[6]

This pathway might play a role in exacerbating pain and sensitivity to light during migraines by affecting the pupillary response to light. These mechanisms suggest that light sensitivity in migraines could be due to an interplay between the visual system and pain pathways, leading to the heightened photophobia commonly seen during attacks. [7] Pupillary abnormalities as a potential cause of migraine with photophobia, and the relationship between pupil size and migraine severity, have not been widely investigated.[8] While treatments like tinted glasses and blue light

filters have been suggested—due to the fact that certain wavelengths of light are known to trigger migraine attacks—the possible role of a larger pupil size as a trigger factor for migraines has not been explored.[9] This study aims to fill that gap by comparing the pupil sizes of patients with migraines and photophobia to those of normal subjects, and by correlating pupil size to the severity of headache. Understanding whether larger pupil size contributes to migraine onset could open new avenues for managing migraines, particularly those triggered or worsened by light.

Methods

This prospective case-control study was conducted at Swaminarayan Institute of Medical Sciences and Research, a tertiary-level hospital located in Kalol, Ahmedabad. It included a total of 100 eyes from 50 patients, aged 20–30 years, who experienced migraines with photophobia. The male-to-female ratio among the participants was 40:60. An equal number of age- and sex-matched individuals without a history of headaches were included in the control group. All participants provided informed consent prior to their inclusion in the study. This design aimed to ensure a balanced comparison between the migraine and control groups, allowing for an examination of the potential role of pupil size in migraine severity. All participants in both the case and control groups had normal vision (6/6 visual acuity) without significant refractive errors. Intraocular pressure (IOP) was measured for all subjects and found to be within the normal range. Both anterior and posterior segment evaluations of the eyes were normal for all participants, ensuring that no underlying eye conditions influenced the results.

To classify migraines, the study followed the International Classification of Headache Disorders (ICHD-3) criteria. Migraine patients with photophobia completed the Migraine Disability Assessment (MIDAS) test questionnaire, which helped assess the severity of their condition. Additionally, the side of the headache (whether unilateral or bilateral) was also inquired from all migraine patients, ensuring a detailed assessment of their condition.

Pupil size was measured in all participants while their pupils were undilated, using the IOL Master 700**.** Measurements were taken under normal bright light conditions (photopic conditions) to ensure consistency. A single observer performed the measurements for both the migraine patients and the control group to reduce variability. The lighting conditions remained constant throughout the study for all participants. None of the participants were on any eye drops or medications prior to the study, ruling out any external influences on pupil size. Additionally, all participants underwent a neurological examination before the study, and results were normal, ensuring no underlying neurological conditions that could affect the findings.

Results:

In this study, the mean pupil size for patients with migraine and photophobia was 4.89 mm ± 0.91 mm (95% confidence interval). For the control group of normal subjects, the mean pupil size was 3.8 mm ± 0.49 mm (95% CI). The difference in pupil size between the two groups was found to be statistically significant, with a P value of <0.0001, indicating that the larger pupil size in migraine patients is highly unlikely to be due to chance and may be linked to the condition. This suggests a potential physiological difference in pupil response in individuals with migraines and photophobia (Table1)

Among the 50 patients with migraine, the severity of disability was categorized using the Migraine Disability Assessment (MIDAS) test. The distribution of patients across the four grades of disability was as follows: Grade 4 (severe disability): 20 patients with a mean pupil size of 5.6 mm ± 0.79 mm. Grade 3 (moderate disability): 15 patients with a mean pupil size of 4.6 mm ± 0.68 mm. Grade 2 (mild disability): 10 patients with a mean pupil size of 4.26 mm ± 0.44 mm. Grade 1 (minimal disability): 5 patients with a mean pupil size of 3.95 mm ± 0.58 mm. (Table2) The study found that the pupil size was largest in patients with the most severe disability (Grade 4), and progressively smaller in patients with less severe disability, suggesting a correlation between larger pupil size and greater migraine severity. This pattern highlights the potential link between pupil size and the intensity of migraine symptoms.

In the study, it was observed that in 80% of patients, the larger pupil size corresponded with the side frequently associated with migraine attacks. In the remaining 20%, both sides exhibited a similar frequency of migraine attacks. While the pupil reaction time to light appeared to increase with larger pupil sizes, this specific measurement was not quantified in this study. Near vision was assessed and found to be normal among the participants, with none of them reporting difficulties in near vision. Notably, the largest pupil diameters recorded in the study were 7.2 mm and 6.8 mm in a single patient who experienced severe photophobia and reported migraine attacks triggered by exposure to sunlight. This patient's sensitivity to light led to a preference for staying indoors, highlighting the significant impact of photophobia on quality of life for migraine sufferers.

Table 1: mean pupil size (mm) in patients of migraine versus normal subjects

	Migraine with photophobia	No headache
Mean photopic pupil size (in mm)	4.89+0.91 mm	3.8+0.49 mm

Table 2: mean pupil size (mm) migraine patients with different grades of severity

MIDAS grades of migraine severity	Mean photopic pupil size (in mm)
Grade 1	3.95+0.58 mm
Grade 2	4.26+0.44 mm
Grade 3	4.6+0.68 mm
Grade 4	5.6+0.79 mm

Discussion

Migraine is one of the oldest recognized diseases and is a debilitating condition that affects more than 1 billion people worldwide. It typically presents as recurrent attacks of moderate to severe headaches that are often localized to one side of the head.[10] Accompanying symptoms frequently include nausea, as well as hypersensitivity to light (photophobia) and sound (phonophobia). In fact, photophobia is a core component in 80% of migraine cases, which significantly impacts the quality of life and results in the loss of productive hours for those affected.[11] While various treatment modalities are available for managing migraines, the complexity of the condition—due to its multifaceted nature and the presence of multiple triggers—makes complete treatment challenging. This highlights the importance of ongoing research into understanding the mechanisms of migraine, as well as the need for individualized treatment approaches to effectively manage symptoms and improve the quality of life for those affected.[12]

The underlying cause of photophobia in migraines remains poorly understood, although several theories involving various neural circuits have been proposed. A consistent finding in the literature is the dysfunction of the autonomic nervous system. Instances of transient, unilateral mydriasis (dilation of the pupil) have been reported in patients with a history of migraines, sometimes resembling Adie's-like tonic pupil, which may be triggered by migraine episodes. While mydriasis that persists beyond the duration of migraine attacks is rare, some cases have been documented. For instance, in a study by Barriga et al., nine patients with typical hemicranial migraines developed ipsilateral mydriasis during an attack, which outlasted the migraine episode and persisted independently of subsequent attacks. These findings suggest possible ciliary ganglionic dysfunction**.** [13] The relationship between severe migraines with photophobia and pupil size—whether individuals inherently have larger pupils or if this develops as a secondary effect of migraine—has not been extensively researched. However, one report highlighted a patient who had no previous headaches but developed an Adie's pupil after a road traffic accident, followed by severe migraines with intense photophobia. This patient experienced significant relief from both photophobia and migraines after receiving 0.125% pilocarpine drops**,** indicating that targeted therapy may alleviate migraine. [14]

In this study, pupillary size measurements were compared between cases (migraine patients with photophobia) and controls using the IOL Master 700**,** marking it as one of the first studies of its kind. The IOL Master 700 was utilized to measure photopic pupil size, and measurements were taken by a single observer under consistent lighting conditions to ensure accuracy and minimize variability. The use of the IOL Master 700 for measuring pupil size offers several advantages, including ease of use, high reproducibility, and reliability of the measurements. This is crucial for drawing valid comparisons between groups. Supporting this, an article by Ryu and Shin demonstrated that pupil size comparisons made with the IOL Master 700 had good reproducibility when compared to a video pupillometer, further validating the methodology employed in this study.[15] These factors enhance the credibility of the findings and underscore the potential significance of pupil size as an indicator of migraine severity and photophobia in affected individuals.

Given that migraine is a multifactorial condition with numerous potential confounding factors, this study specifically included patients whose predominant complaint was photophobia associated with migraines. Exclusion criteria were strict, eliminating patients with any refractive errors, convergence weakness, squint, ocular pathologies, history of trauma, neurological conditions, or systemic diseases. Subjects exhibiting anisocoria (unequal pupil sizes) were also excluded, with only a maximum difference of 0.4 mm between the pupil sizes considered physiological. The study focused on measuring pupil size in normal ambient lighting conditions using the IOL Master 700 for both cases and controls, rather than comparing pupil sizes in dark conditions or under bright light stimulation.[16] The findings revealed that patients with migraines and photophobia had larger pupil sizes compared to those without a history of headaches. Additionally, there was a correlation between MIDAS scores and pupil size; the more severe the MIDAS score, the larger the pupil size. Importantly, it was noted that

in 80% of patients, the side with the larger pupil size corresponded with the side frequently associated with migraine headaches. This observation warrants further investigation with a larger patient cohort to determine whether pupil size is a trigger for migraine attacks linked to photophobia. If a causal relationship is established, it may lead to innovative approaches to reduce attack frequency by modifying light exposure to the eyes. This could significantly enhance the management strategies for individuals suffering from migraines with photophobia.[17] In this study, all patients who exhibited larger pupil sizes were advised to use photochromatic antireflective glasses. The goal of this intervention is to assess whether these glasses can help reduce the impact of light sensitivity and, consequently, the severity of migraines over time. Their MIDAS scores will be evaluated after 3 months to determine any changes and assess the effectiveness of this approach.

Initial follow-up data from about 30 patients after 1 month showed a significant reduction in headache frequency and severity. However, to conduct a comprehensive pre- and post-intervention analysis, the 3-month data will be crucial. This extended assessment will provide a clearer picture of the impact of the photochromatic glasses on both headache severity and quality of life for patients suffering from migraines with photophobia.

Conclusion

The findings of this study indicate that patients with migraines accompanied by photophobia exhibit larger pupil sizes compared to individuals with no history of headaches. Moreover, there is a direct correlation between the severity of headaches and the size of the pupils; as the severity increases, so does the pupil size. These observations highlight the need for targeted therapies aimed at reducing the amount of light reaching the retina. Such interventions could potentially decrease the frequency of migraine attacks and improve the overall quality of life for patients suffering from migraines with photophobia.

Further extensive research is essential to explore these relationships more deeply, particularly regarding the mechanisms behind pupil size in relation to migraine triggers. Investigating the efficacy of various light-reducing interventions could pave the way for more effective management strategies in this patient population.

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