Retinal Nerve Fiber Layer Analysis in Children with Migraine with and without Aura using Optical Coherence Tomography: A Case-Control Study

Daniela Rego-Lorca (✉ dpregolorca@gmail.com)  
Hospital Clinico Universitario San Carlos  
https://orcid.org/0000-0002-8076-0522

Barbara Burgos-Blasco  
Hospital Clinico Universitario San Carlos

Cristina Gines-Gallego  
Hospital Clinico Universitario San Carlos

Mario Carrasco-Lopez-Brea  
Hospital Clinico Universitario San Carlos

Maria Teresa de Santos- Moreno  
Hospital Clinico Universitario San Carlos

Enrique Santos-Bueso  
Hospital Clinico Universitario San Carlos

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Abstract

Purpose

To evaluate retinal nerve fiber layer (RNFL) thickness in children with migraine, with and without aura, compared to healthy controls using optical coherence tomography (OCT).

Methods

Cross-sectional case-control study. Peripapillary RNFL thickness was measured using optical coherence tomography (OCT) in a group of children diagnosed with migraine with aura (MwA) (n=9) and migraine without aura (MwoA) (n=11), and in a group of healthy controls (n=20). Age, sex, duration of migraine in months, number of episodes per month, duration of episodes in hours, and use of prophylactic treatment with magnesium were recorded. Groups were matched by age, sex and refractive error. All participants underwent complete neurological and pediatric examination.

Results

No significant differences were found when comparing all migraine patients with healthy controls. However, children with MwA showed statistically significant reductions in RNFL thickness in the temporal (mean difference 7.83; CI95% 0.52-15.14, P=0.027) and inferior-temporal (mean difference 16.06; CI95% 1.95-30.16, P=0.027) sectors compared to patients with MwoA. None of the other sectors showed statistically significant differences between groups (all P>0.05).

Conclusion

Aura in migraine may be associated with a RNFL thickness decrease in children.

Introduction

Migraine is a common chronic disorder characterized by recurrent episodes of primary headache, having a high impact among children. Its prevalence in this population group is up to 10%, migraine being the most frequent cause of persistent headache in childhood.[1]

According to the International Classification of Headache Disorders, migraine can be classified into two main groups: migraine with aura (MwA) and migraine without aura (MwoA).[2] The term aura refers to the transient focal neurological symptoms that may anticipate or accompany the headache. It appears in around 25% of patients, frequently manifesting as transient ophthalmological symptoms such as blind spots, light flashes, or photophobia.[3]

Although the pathophysiology of migraine is still not completely understood, evidence to date suggests a neurovascular dysfunction leading to vasospasm of cerebral and retrobulbar vessels. This repeated reduction in blood flow, although transient, is believed to cause structural damage to the brain.[4]
Fluctuations in perfusion concerning optic nerve head (ONH) microcirculation could thus contribute to ganglion cell death and retinal nerve fiber layer (RNFL) changes in patients with migraine. In fact, migraine has been recognized as a risk factor for some ophthalmic disorders, such as ischemic optic neuropathy or normal-tension glaucoma.[5]

Optical coherence tomography (OCT) is a rapid non-invasive imaging technique that provides reliable measurements of RNFL thickness. It has been used to evaluate neurodegeneration in neurological diseases.[6–10] In Parkinson's disease, several studies refer peripapillary RNFL thinning[10] and Chorostecki et al.[9] also noticed diminished thickness of macular inner retinal layers.

Even though several studies, many of them OCT-based, concerning ophthalmological changes in patients with migraine have been published, the vast majority of them have been performed in adult population.[3] Articles evaluating OCT changes in children with migraine are scarce, and, in those studies, contradictory results have been reported.[11, 12] Also, among the latter, none of them assess differences between MwA and Mwo children.

Hence, the aim of the present study was to evaluate RNFL thickness changes in children with migraine comparing to healthy controls, and analyse RNFL changes in the former group depending on their type of migraine.

Materials And Methods

This observational cross-sectional case-control study was conducted at the Ophthalmology Department of Hospital Clínico San Carlos, Madrid, Spain. Migraine patients were consecutively recruited at the Pediatric Neurology Department of Hospital Clínico San Carlos. Patients with a diagnosis of migraine, with or without aura, according to criteria of the International Classification of Headache Disorders, 3rd Edition (ICDH-3)[2], were considered. Healthy controls were recruited at the Pediatric Ophthalmology Department, where they came for a routine follow-up visit. Controls were matched by age, sex and refractive error.

Inclusion criteria for migraine patients comprised being under 18-years-old, diagnosis of migraine, with or without aura, according to criteria of the ICHD-3, and voluntary acceptance to participate in the study. Exclusion criteria included any neurologic disorder other than migraine, retinal and optic disc pathology, history of intraocular surgery, ocular hypertension, and refractive errors with spherical equivalent higher than ±3 dioptres.

Among demographic and clinical variables, sex, age, duration of migraine (months), frequency of attacks (episodes per month), episode duration (hours), and use of prophylactic treatment with magnesium were recorded.

All subjects underwent complete neurological and pediatric examination. Ophthalmological exam included best corrected visual acuity, slit lamp biomicroscopy, fundus examination and intraocular
pressure measurement. Optic nerve OCT images were obtained using Heidelberg Spectralis OCT (Heidelberg Engineering, Heidelberg, Germany) in SD-OCT mode. Mean global RNFL thickness and the average thickness for each sector of the ONH (temporal, superior-temporal, inferior-temporal, nasal, superior-nasal, and inferior-nasal) were noted, all of which were automatically produced by the software.

All subjects were evaluated by the same ophthalmologist and only one eye per patient was included, randomly selected when both eyes met the inclusion criteria.

The Clinical Research Ethics Committee at Hospital Clínico San Carlos, Madrid, Spain, approved the study protocol, which adhered to the Declaration of Helsinki. Informed consent was obtained from all patients and their parents.

Statistical analysis was performed using SPSS software for Mac (SPSS, Inc. Chicago, USA, version 22). Values are expressed as mean ± standard deviation (SD) and absolute frequency (n) and relative frequency (%) where appropriate. Student’s t-test was used to examine differences among groups. Spearman test was used to investigate correlations Statistical significance was set at P < 0.05.

**Results**

The initial study population comprised of 20 children with migraine, 11 of them diagnosed with migraine without aura (MwoA) and 9 with migraine with aura (MwA), and 20 healthy controls. Among the migraine patients, 3 were finally excluded (2 patients with MwoA and 1 with MwA). The 2 MwoA patients were excluded because of associated ophthalmic pathology: juvenile idiopathic arthritis associated uveitis and optic nerve drusen, respectively. The MwA patient was excluded due to lack of collaboration.

Table 1 portrays the demographic and clinical variables of the case group (n=17). Mean age was 13.8 ± 2.9 years in patients with migraine and 13.4 ± 2.5 years in healthy individual. Male to female ratio was 7:10 in migraine patients and 8:12 in healthy controls. No differences in sex and age were detected between groups (p<0.05)

Among the RNFL sectors, no significant differences were found when comparing all migraine patients with healthy controls (table 2). However, patients with MwA showed statistically significant decreases in temporal (mean difference 7.83; CI95% 0.52-15.14, P=0.037) and inferior-temporal (mean difference 16.06; CI95% 1.95-30.16, P=0.027) RNFL thickness compared to patients with MwoA (figure 1). None of the other sectors showed statistically significant differences between groups (all P>0.05).

No correlations between RNFL sectors and clinical variables (episodes per month and episode duration) were found in the migraine group when Bonferroni corrections were applied (all P>0.05).

**Conclusions**
Migraine, which is the most common cause of recurring headache in children, has a high risk of becoming a chronic condition persisting in adulthood.[13] Despite its high prevalence and socioeconomic impact, the exact mechanism causing migraine attacks is still not understood. Studying migraine patients with OCT, to evaluate changes in the optic nerve and different retinal layers, could promote a better understanding of the pathophysiology of migraine. Our results reveal that, despite noting no differences when comparing migraine patients with healthy controls, children with MwA have thinner RNFL thickness in some specific OCT sectors compared with children with MwoA.

Regarding adult population, published data on OCT changes in migraine patients have yielded variable results. In a meta-analysis of published case-control studies, Feng et al.[14] described decreased peripapillary RNFL thickness (average and all individual quadrants) measured with OCT in migraine patients compared to healthy controls. However, other authors have only found differences in RNFL thickness when comparing specific sectors. For instance, Colak et al.[15] found thinner RNFL in the superior and inferior quadrants of migraine patients compared to healthy controls. Similarly, Kirbas et al.[16] found significant differences regarding the superior quadrant, while Sorkhabi et al.[17] and Demircan et al.[18] just reported differences in the nasal quadrant. Martinez et al.[19] results show differences only in the temporal sector. On the other hand, Tan et al.[20] reported similar RNFL thickness in migraine patients and healthy controls, with no statistical difference between groups.

As for the pediatric population, available literature in this regard is scarce. Dereli Can et al.[12] performed a case-control study using optical coherence tomography angiography (AOCT) and found no significant difference in peripapillary RNFL thickness, neither average nor for individual quadrants, between children with migraine and healthy controls. Foveal avascular zone (FAZ) and the capillary vessel density (CVD) analysis also yielded no differences between groups. Yener et al.[11] published a case-control study comparing the peripapillary RNFL thickness, the macular ganglion cell layer (GCL) thickness and ONH parameters between children with migraine and healthy controls. While they did not find any significant differences regarding the GCL thickness, their results reveal thinner RNFL in the temporal quadrant of the left eyes of the migraine patients compared to the healthy controls, but thicker RNFL in the nasal quadrant of both eyes of the migraine group. In our study, similarly to Dereli Can et al.[12], we did not find any significant difference in the average RNFL thickness or in any specific OCT sector between the children with migraine group and the healthy controls.

Furthermore, some authors have classified adult migraine patients in subgroups of MwA and MwoA, being statistically significant lessening of RNFL thickness more frequently found in MwA patients.[3] Ekinci et al.[21] compared RNFL, GCL and choroid thickness in patients with MwA, MwoA and controls, and found that, although choroid was thinner in both subgroups of migraine patients, RNFL and GCL were significantly thinner in MwA patients as compared with both the MwoA group and the healthy controls. Along the same lines, Chang et al.[22] found decreased vascular density in the superficial fovea and superior peripapillary region in MwA, but not in MwoA patients. Simsek[23] found thinner RNFL in migraine patients with white matter lesions (WML), those being detected in magnetic resonance imaging (MRI) in relation with chronic ischemia, in comparison with healthy controls and with migraine patients.
without WML. Even though the exact mechanism causing WML remains unclear, their detection in MRI has been associated with aura. However, while significant changes have been observed among adults, no studies are found evaluating differences between MwA and MwoA in pediatric population. Our results, when comparing these two groups, show statistically significant thinner RNFL thickness in the temporal and the inferior-temporal quadrants of the MwA compared to MwoA patients.

Some authors have investigated the correlation between OCT changes and migraine clinical variables, such as frequency of attacks or disease duration. Controversial results have been noted concerning the influence of the frequency of migraine attacks. Whereas Gipponi et al. defended that there is no relationship between frequency of migraine attacks and RNFL thickness, Reggio et al. observed an inverse association between the number of monthly migraine attacks and RNFL thickness. Also, different conclusions have been reached when studying the association of the length of migraine history with RNFL thickness. Gipponi et al., analogous to their findings regarding frequency of migraine, referred no influence of illness duration on RNFL thickness. On the contrary, Feng et al. found that longer migraine history was associated with significantly thinner RNFL. Finally, as for influence of migraine severity, Dereli Can et al. reported a significant inverse correlation between the pediatric migraine disability assessment test (PedMIDAS) grade and the average RNFL thickness and the peripapillary CVD. In our study, duration of migraine did not have significant influence on RNFL thickness changes although larger samples are mandatory to rule out associations.

Although pathophysiology of migraine is not fully understood to date, a neurovascular mechanism is the most widely accepted hypothesis. Migraine attacks involve activation of the trigeminovascular system (TGVS), responsible for vascular tone regulation and pain transmission. The TGVS innervates intra- and extra-meningeal blood vessels, the brain stem and some extracranial tissues, including ocular structures. Activation of the TGVS results in vasoactive neurotransmitters being released, causing vascular and inflammatory changes that result in pain. These neurovascular changes would motivate cerebral and retrobulbar vessels vasospasm, with subsequent focal hypoperfusion. The latter is specially observed in patients with higher frequency of migraine attacks and in MwA patients. Despite being a transitory condition, this blood flow reduction is believed to constitute a risk factor for structural brain damage and even damage to other regions, such as the retina or the optic nerve. Retinal damage due to focal ischemia would result in a diminished RNFL thickness, reflecting a reduced number of axons in these patients. Thus, the fact that hypoperfusion and chronic ischemia, leading to central nervous system and retinal damage, are more frequently observed in MwA patients could explain our results showing significantly diminished RNFL thickness in some OCT sectors in MwA patients compared to the MwoA group.

The study has several limitations. First, our study included a relatively small sample size. Hence, differences according to migraine characteristics could not be thoroughly analyzed. In addition, longitudinal testing with repeat imaging at fixed intervals could provide valuable information regarding both the short- and long-term effects of migraine on the RNFL. Finally, although we demonstrated statistically significant thickness differences, the clinical relevance of this finding is unclear.
In conclusion, our study reports a statistically significant reduction in RNFL thickness in MwA, being this the first study to investigate differences between MwA and MwoA in the pediatric population. Notwithstanding, further studies are needed to establish the significance of these results and evaluate long-term consequences.

**Declarations**

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**Conflicts of interest**

The authors have no relevant financial or non-financial interests to disclose.

**Ethics approval**

The Clinical Research Ethics Committee at Hospital Clinico San Carlos, Madrid, Spain, approved the study protocol, which adhered to the Declaration of Helsinki.

**Consent to participate**

Informed consent was obtained from all patients and their parents.

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Tables

| Characteristics                  | Migraine patients (n = 17) | Healthy individuals (n = 20) |
|---------------------------------|---------------------------|-----------------------------|
| Age (years)                     | 13.8 ± 2.9                | 13.4 ± 2.5                  |
| Sex                             |                           |                             |
| Male                            | 7 (41%)                   | 8 (40%)                     |
| Female                          | 10 (59%)                  | 12 (60%)                    |
| Type of migraine                |                           |                             |
| Without aura                    | 9 (53%)                   | -                           |
| With aura                       | 8 (47%)                   | -                           |
| Duration of migraine (months)   | 31.6 ± 37.2               | -                           |
| Frequency of attack (episodes/month) | 3.7 ± 7.7           | -                           |
| Episode duration (hours)        | 14.2 ± 18.1               | -                           |
| Treated with magnesium          | 5 (29%)                   | -                           |
Table 2
Differences in peripapillary retinal nerve fiber layer (RNFL) thickness measured using optical coherence tomography in migraine patients and healthy controls.

| RNFL             | Healthy | Migraine | p (healthy vs migraine) | Migraine without aura | Migraine with aura | p (migraine without aura vs with aura) |
|------------------|---------|----------|-------------------------|-----------------------|--------------------|----------------------------------------|
|                  | 101.70 ± 10.29 | 101.97 ± 9.99 | 0.909                  | 104.67 ± 10.14        | 98.94 ± 9.19       | 0.096                                  |
| Global           |         |          |                         |                       |                    |                                        |
| Temporal         | 76.05 ± 14.82 | 73.65 ± 11.02 | 0.438                  | 77.33 ± 10.19         | 69.50 ± 10.72      | 0.037*                                 |
| Superior-temporal| 139.60 ± 24.50 | 147.21 ± 21.24 | 0.162                  | 151.83 ± 20.07        | 142.00 ± 21.95     | 0.182                                  |
| Inferior-temporal| 141.78 ± 18.22 | 147.00 ± 21.45 | 0.261                  | 154.56 ± 13.63        | 138.50 ± 25.61     | 0.027*                                 |
| Nasal            | 72.98 ± 17.05 | 70.76 ± 11.16 | 0.512                  | 69.61 ± 9.94          | 72.06 ± 12.60      | 0.531                                  |
| Superior-nasal   | 118.50 ± 28.21 | 120.26 ± 21.41 | 0.766                  | 119.78 ± 21.41        | 120.81 ± 23.15     | 0.891                                  |
| Inferior-nasal   | 116.00 ± 25.00 | 113.68 ± 23.57 | 0.683                  | 117.17 ± 29.68        | 109.75 ± 13.90     | 0.368                                  |

Figures

![Optic nerve parameters in patients with migraine](image)

Figure 1
Peripapillary retinal nerve fiber layer (RNFL) thickness measured globally and in different sectors in children with migraine, comparing those with and without aura. OCT: optical coherence tomography. RNFL thickness is measured in μm. * indicates p<0.05.