Análisis de la capa de fibras nerviosas de la retina con tomografía de coherencia óptica en niños con migraña

Analysis of the retinal nerve fiber layer in children with migraine using optic coherence tomography

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RESUMEN

Objetivo: El propósito de este estudio fue encontrar anomalías estructurales en la capa de fibras nerviosas de la retina (CFNR) de niños y adolescentes con migraña.

Métodos: Este estudio incluyó a 50 pacientes en el grupo migraña, 25 con aura visual y 25 sin aura, y 25 sujetos en el grupo control. Se usó la tomografía de coherencia óptica de dominio espectral para medir y comparar el grosor de la CFNR entre los grupos migraña y control.

Resultado: Hubo una diferencia significativa en el grosor medio de la CFNR (ojo derecho, OD = $p < 0{,}013$; ojo izquierdo, OI = $< 0{,}019$). y en los cuadrantes nasal (OD = $p < 0{,}001$; OI = $p < 0{,}001$) y temporal (OD = $p < 0{,}001$; OI = $p < 0{,}001$) en el grupo migraña en comparación con el control. Al comparar el subgrupo migraña con aura con el subgrupo migraña sin aura se encontró una diferencia estadísticamente significativa en el grosor de la CFNR en cuadrantes superior (OD = $p < 0{,}004$; OI = $p < 0{,}003$), temporal (OD = $p < 0{,}008$; OI = $p < 0{,}001$) y nasal (OD = $p < 0{,}001$; OI = $p < 0{,}001$).

Conclusiones: Este estudio sugiere que la migraña provoca una reducción del grosor de la CFNR peripapilar.

Palabras clave: Adolescentes. Niños. Migraña. OCT. CFNR.

ABSTRACT

Aim: The purpose of this study was to find structural abnormalities in the retinal nerve fiber layer (RNFL) of children and adolescents with migraine

Methods: This study included 50 patients with migraine , 25 with visual aura and 25 without, and a control group of 25 subjects. Spectral domain optic coherence tomography was used to measure and compare RNFL thickness between the migraine and control groups.

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Results: There was a significant reduction in the average RNFL thickness (oculus dexter, OD = $p < 0.013$; oculus sinister, OS = < 0.019) and that of the nasal (OD = $p < 0.001$; OS = $p < 0.001$) and temporal quadrants (OD = $p < 0.001$; OS = $p < 0.001$) in the migraine group compared to those of the control one.. Also comparing the migraine with aura subgroup to the migraine without aura subgroup , there was a statistically significant difference in RNFL thickness parameters according to the superior (OD = $p < 0.004$; OS = $p < 0.003$), temporal (OD = $p < 0.008$; OS = $p < 0.001$) and nasal sectors (OD = $p < 0.001$; OS = $p < 0.001$).

Conclusions: This study suggests that migraine leads to a reduction in the peripapillary RNFL thickness.

Keywords: Adolescent, children, migraine, OCT, RNFL

BACKGROUND

Migraine headache frequently occurs in children and adolescents and is one of the most common diseases of childhood with a prevalence of 9.1 % (1). In almost 30% of people with migraine, the headache is preceded by a wide range of neurological symptoms (visual, motor, or somatosensory) known as *aura*, and which can last between 5 to 60 minutes or sometimes for several days (2,3). Migraine can be clinically subdivided into two major groups: migraine with aura (MWA) and migraine without aura (MWoA) (4). It differs from migraine in adults in that the headache is bilateral, gastrointestinal symptoms are more prominent and the attacks may beshorter and last between 1 and 72 hours. Due to these features, itis also likely to be under-diagnosed (3,5,6).

The pathogenesis of migraine remains unclear. Focal reduction of blood flow reported in migraine attacks, particularly in MWA, most commonly starts in posterior circulation, that is to say, within the vascular territory supplied by the vertebrobasilar system (7). Rarely, hypoperfusion arises from other parts of the brain in cluding the retina (6-8). Retinal strokes caused by retinal artery occlusions have been reported in migraine patients (8,11). Although the vasoconstriction of cerebral and retinal blood vessels is a transient phenomenon, the chronic nature of migraines could lead to permanent structural abnormalities through less intense hypoperfusion phenomena (10,12-14). In one study by Kara et al. in which Doppler ultrasound was used to demonstrate retinal vascular changes and perfusion on adult migraine patients, they found that the resistance in the central retinal artery and posterior ciliary artery was higher in migraine patients than in the control group during intercritic periods (15).

An alteration of the quality of perfusion in the optic nerve head or in the retina may lead to ganglion cell death in migraine patients (16,17). Retinal nerve fiber layer (RNFL) thickness measurements can be used as an index to assess ganglion cell and retinal nerve fiber damages.The aim of this study was to compare the RNFL thickness in the eyes of migrainous children and adolescents with healthy controls using spectral-domain optical coherence tomography (OCT).

METHODS

This was a prospective observational study conducted in the Ophthalmology Service of the University Hospital San Juan de Alicante, Alicante, Spain. We studied 100 eyes of 50 consecutive patients (15 male, 35 female; mean age = 9.5 years-old (5-15 yo. range) with migraine using the criteria of the Headache International Society (4). All the patients were referred from the Neuropaediatrics Department of the same hospital. The 50 patients, all Caucasian, were divided into two subgroups: 25 with MWA (10 male and 15 female; mean age = 9.16 yo; range = 5-15 yo.) and 25 MWoA (6 male and 19 female ; mean age = 9.84 yo.; range = 5-15 yo.). The control group consisted of 25 healthy controls (10 male and 15 female; mean age = 9.9 yo.; range = 5-15 yo.). We excluded patients with any prophylactic treatment to avoid possible effects of these drugs on retinal nerve fiber layer thickness.

Written informed consent was obtained from the parents of participating minors. The project was approved by the Research Ethics

Board at The University Hospital San Juan de Alicante, and conducted in accordance with the Tenets of Helsinki.

All patients underwent complete neurological and paediatric exam which excluded any other origin of the headache than the migraine. The ophthalmologic exam included the following tests: best-corrected visual acuity (using Snellen charts), slit-lamp biomicroscopy, dilated funduscopic examination with a 90-diopter lens, axial length (AL), and manifest refraction and cycloplegic refraction after pupillary dilation with one drop of cyclopentolate 1%. All children with a spherical equivalent more myopic than –2.00 diopter and more hyperopic than +3.00 were excluded. Ocular axial lengths was measured using an corneal biometry device (OcuScan® RxP; Alcon, Forth Worth, Texas, USA). Patients with a history of intraocular surgery, retinal or neurological disease, nystagmus, glaucoma, laser treatment, or cataract and patients not sufficiently cooperative to undergo an optical coherence tomography examination were excluded. Each subject was imaged three times with SD-OCT (Topcon 3D OCT-2000, Japan, protocol 3D-Disc cube) to evaluate peripapillary RNFL thickness and the mean values were recorded. All scans were performed by the same operator through dilated pupils. An internal fixation target was also used in all scans with the realtime eye tracking system to adjust for eye motion. SD-OCT measurements were taken at the same time of the day to minimize the effects of diurnal variation.

The SD-OCT scan protocol used to evaluate RNFLwas calculated by the optic disc cube 512 x 128 (128 horizontal scan lines comprised of 512 A-scans, in a 6 x 6 mm area) with a maximum scan velocity of 50.000 axial scans/second. Parameters including average RNFL thickness in four quadrants were generated automatically in the analysis report. The average and four-quadrant RNFL thickness data –temporal, superior, nasal and inferior– were collected and compared insidethe migraine group –that is to say, MWA group versus MWoA group. Then, combined data from the migraine group (MWA+MWoA) were also compared to the control group. In addition, we calculated the correlations among average RNFL thickness and age, sex and the migraine duration from diagnosis (fig. 1).

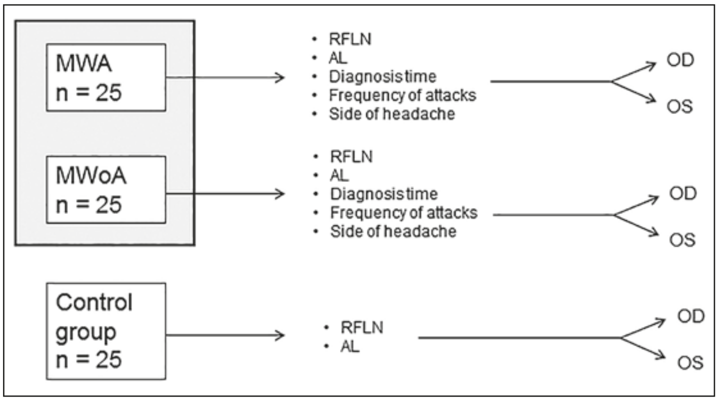

Fig. 1: Materials and methods. MWA (Migraine with Aura), MWoA (Migraine without Aura), RNFL (Retinal Nerve Fiber Layer), AL (Axial length).

The statistical analysis was perfomed using the Statistical Package for Social Sciences (SPSS) program version 20.0, for Windows (SPSS, Chicago, IL, USA). Data were reported as the mean ± standard deviation (SD). The normality of the distribution for all variables was assessed by the Kolmogorov-Smirnov test. Student's t-test was used for the comparison of normally distributed variables and Mann-Whitney U test was used for nonparametric variables between the two groups. Relationships between variables were analyzed by Pearson or Spearman correlation analysis according to the distribution type of the variables. Differences were considered significant if theyexceed the 95% confidence interval.

RESULTS

According to the demographic features, there were no statistically significant differences between patients with migraine and the control group in sex and age. Within the migraine group, 25 had MWA and 25 MWoA. No significant difference was found between the two migraine subgroups in demographic features and clinical characteristics of headache (table 1).

Average RNFL thickness was 92.60 ± 6.64 µm in OD and 92.44 ± 5.97 µm in OS of the MWA subgroup; the difference was statistically insignificant (p 0.929). There were no statistically significant differences in average RNFL thickness of the right and left eyes in the MWoA subgroup (OD = 104.56 ± 7.84 vs OS = 104.72 ± 7.51 µm ; p 0.942). In the same way, there were no statistically significant differences in average RNFL thickness

Table I: Clinical characteristics of migraine subgroups

Variable	Migraine with aura	Migraine without aura	p-value*
Diagnosis time (year)	1.88 ± 1.22	2.36 ± 1.06	0.704
Frequency of attacks (month)	2.8 ± 1.6	3.1 ± 1.6	0.694
Unilateral	16	14	0.314
Bilateral	9	12	0.314

of the right and left eyes in the control group (OD = 99.92 ± 6.3 vs OS = 100.84 ± 7.1 µm; p 0.689).

The migraine group (MWA+MWoA) compared to the control group showed a statistically significant difference in RNFL thickness parameters according to the temporal (OD = 77.42 ± 10.6 vs 121.64 ± 15.2 µm; p < 0.01. OS = 75.22 ± 13.4 vs 125.6 ± 16.5; p < 0.01) and inferior (OD = 120.11 ± 17.1 vs 80.92 ± 17.12 µm; p < .01. OS = 126.34 ± 13.7 vs 80.68 ± 21.37; p < 0.01) sectors.There were no statistically significant differences in the other RNFL thickness parameters and axial length between the two groups (table II).

The MWA subgroup and the MWoA subgroup showed a statistically significant difference in average RNFL thickness (OD = 92.6 ± 6.64 vs 104.5 ± 7.84 µm; p < 0.01. OS = 92.44 ± 5.97 vs 104.72 ± 7.5; p < 0.001) and according to the superior (OD = 115.9 ± 15.9 vs 128.64 ± 13.9 µm; p 0.004. OS = 113.0 ± 19.9 vs 123.36 ± 13.64; p < 0.01), inferior (OD = 111.16 ± 15.33 vs 127.04 ± 10.01 µm; p < 0.01. OS = 117.68 ± 10.59 vs 135 ± 10.68; p < 0.01) and nasal (OD = 68.24 ± 12.3 vs 82.0 ± 12 µm; p < 0.01. OD = 69.2 ± 16.82 vs 83.88 ± 10.03 µm; p 0.001) sectors. There were no statistically significant differences in the other RNFL thickness parameters and axial length between the MWA subgroup and the MWoA subgroup (table III).

Average RNFL thickness was 97.72 in boys and 98.88 in girls. There were no statistically significant differences between the sexes. There was a significant correlation between age and average RNFL thickness for both sexes (r 0.245; p 0.014). Therefore, greater RNFL thickness was detected with increasing patient age (fig. 2).

Table II: Comparison of retinal nerve fiber layer (RNFL) thickness in migraine and control groups

Variable	Migraine (n=50)[a]	Control (n=25)[a]	p-value*
OD AL (mm)	22,95 ± 0.8	23,10 ± 0.8	0.457
OD RNFL average, ɥm	98.92 ± 9.3	99.92 ± 6.3	0.631
OD RNFL superior, ɥm	122.22. ± 16.1	122.80 ± 10.1	0.870
OD RNFL inferior, ɥm	120.11 ± 17.1	80.92 ± 17.12	0.001*
OD RNFL temporal, ɥm	**77.42 ± 10.6**	**121.64 ± 15.2**	**0.001***
OD RNFL nasal, ɥm	**75.56 ± 12.8**	**76.4 ± 7.6**	**0.763**
OS AL (mm)	22,91 ± 0.8	23,10 ± 0.8	0.239
OS RNFL average, ɥm	98.58 ± 9.14	100.68 ± 7.1	0.317
OS RNFL superior, ɥm	118.18 ± 18	121.76 ± 12.05	0.366
OS RNFL inferior, ɥm	126.34 ± 13.7	80.68 ± 21.37	<0.001*
OS RNFL temporal, ɥm	75.22 ± 13.4	125.6 ± 16.55	<0.001*
OS RNFL nasal, ɥm	76.54 ± 15.6	77.04 ± 8.48	<0.882

OD RNFL: Right eye Retinal nerve fiber layer in right eye; OS RNFL: Left eye Retinal nerve fiber layer in left eye.*p < 0.05 [a] Values are mean ± SD.

Table III: Comparison of retinal nerve fiber layer (RNFL) in migraine subgroups

Variable	MWA (n=25)[a]	MWoA(n=25)[a]	p-value*
OD AL (mm)	22.97 ± 0.82	22.91 ± 0.81	0.817
OD RNFL average, ɥm	**92.6 ± 6.64**	**104.5 ± 7.84**	**<0.001***
OD RNFL superior, ɥm	115.9 ± 15.9	128.64 ± 13.9	0.004*
OD RNFL inferior, ɥm	**111.16 ± 15.3**	**127 ± 10.01**	**0.001***
OD RNFL temporal, ɥm	75.08 ± 8.8	79.84 ± 11.9	0.115
OD RNFL nasal, ɥm	**68.24 ± 12.3**	**82 ± 12**	**<0.001***
OS AL (mm)	22.9 ± 0.8	22.8	0.692
OS RNFL average, ɥm	**92.44 ± 5.97**	**104,72 ± 7.5**	**<0.001***
OS RNFL superior, ɥm	**113.0 ± 19.9**	**123.36 ± 13.64**	**0.037***
OS RNFL inferior, ɥm	**117.68 ± 10.59**	**135.0 ± 10.68**	**0.001***
OS RNFL temporal, ɥm	72.52 ± 10.41	77.9 ± 15.62	<0.157
OS RNFL nasal, ɥm	**69.2 ± 16.82**	**83.88 ± 10.03**	**<0.001***

OD RNFL: Right eye Retinal nerve fiber layer in right eye; OS RNFL: Left eye Retinal nerve fiber layer in left eye. * p < 0.05[a] Values are mean ± SD.

DISCUSSION

RNFL thickness measurements can be used as a mark in order to assess the ganglion cell damages (16). As a result of ganglion cell damage, a reduction in the thickness of this layer can be expected. OCT is a non-invasive, non-contact imaging technique that renders in vivo cross sectional view of the retina. It enables quantitative assessment of the RNFL thickness around the optic nerve head and is considered a reliable tool for the diagnosis and follow-up of glaucoma and neuroophthalmic diseases (16,17).

As a result of present study, a statistically significant reduction in RNFL thickness measurements of migraine group was detected. The inferior and temporal quadrant RNFL thickness were found to be significantly thinner in the children with migraine compared with that in the control group.

As far as we know, only Nalcacioglu et al. measured RNFL thickness in 40 pediatric migraine patients and compare the values with 40 healthy subjects using SD-OCT; they determined no reduction in the RNFL thickness in any quadrant, and they asserted that migraine had no effect on RNFL (18).

Previous studies in adults using OCT have provided evidence of reduced RNFL thickness in migraine patients, but the results are not completely consistent.

In a study conducted by Martinez et al., RNFL thickness was found to be significantly thinner in the temporal quadrant of migraine patients compared to the control group (19). In another study carried out by Sorkhabi et al. RNFL thickness was only significantly thinner in nasal quadrant in migraine patients compared to the control group (20). Also Demircan et al. found that the mean RNFL thickness for nasal and inferior sectors was significantly thinner in the migraine group than in the control group (21). In another study conducted by Yulek et al., average RNFL thickness in the migraine group was found to be thinner compared to the control group (22). Colak et al. revealed a reduction in the average RNFL thickness in adult migraine patients compared with that in the control group. Similarly, superior and inferior quadrant RNFL thicknesses were significantly lower as well (23). A recent meta-analysis by Feng et al., showed that RFNL thickness decreased in all quadrants in migraine patients compared with the healthy control group (24).

Opposed to the findings of above studies, Tan et al.reported that there was no statistically significant difference in RNFL thickness by using laser polarimetry (25).

In our study, while there was no statistically significant difference in the average, superior and nasal quadrant RNFL thickness measurements between the groups, inferior and temporal quadrant RNFL thickness were found to be significantly thinner in the children with migraine compared with that in the control group.

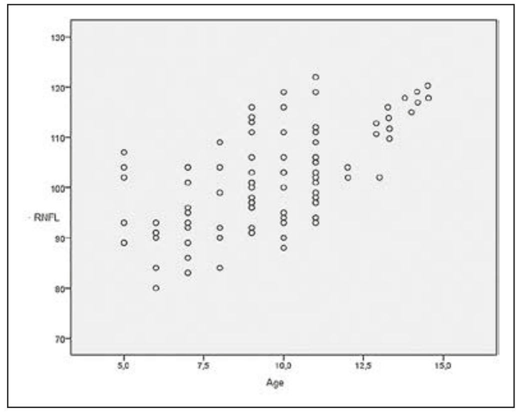

Fig. 2.

Gipponi et al. compared female adult patients with migraine to healthy women, and determined that superior RNFL quadrant was significantly reduced only in migraine patients with aura but not in those without aura (26). Unlike their results, Demircan et al. found no differences between RNFL in migraine with aura and migraine without aura subgroups (21). In our study, when the patients were evaluated as subgroups of migraine with aura and without aura, there was a significant thinning of the average RNFL thickness parameters and according to the superior, inferior and nasal sectors in migraine patients with aura, but no significant differences in in the other RNFL thickness measurements.

In accordance with Sorkhabi et al., Demircan et al. and Gipponi et al, we report that RFNL thickness is independent of headache duration from diagnosis in children with migraine (20,21,26). Besides, there were no statistically significant differences in RNFL thickness between sexes. However, there was asignificant correlation between age and RFNL thickness for both sexes (the greater the age, the more RNFL thickness).

Unlike other studies, we only measured RFNL thickness in migraine patients with and without aura and we compared the results with healthy controls. Attacks of migraine may be linked to hypoperfusion in the retina and optic nerve. The choroid, the vascular layer of the eye, is responsible for most of the ocular blood supply and is vital for the maintainance of the outer retina (27).

Migraine is known to reduce blood flow at the level of the central retinal and posterior ciliary arteries. Demircan et al. and Ekinci et al. report a thinning of the choroid layer in adult migraine patients (21,28). Nevertheless, there are discrepancies between the different studies in relation to choroidal thickness during the migraine attack period. Dadaci et al. and Karalezli et al. reported an increased choroidal thickness during the migraine attack period (28,30) contrary to Dervisogullari et al. and Zengin et al., who reported a reduction in choroidal thickness during the migraine attack period in MWA and MWoA groups (31,32). These differencescould be explained by the fact that both migraine subgroups switch from hypoperfusion to hyperperfusion during their course.

On the other hand, athinning in the RNFL thickness has been reported in adult migraine patients probably due to retinal ischemia. Contrary to the choroidal vessels, the intraocular portion of the retinal vessels has no autonomic innervation. The anterior part of the optic nerve is supplied by the short posterior ciliary arteries and choroidal vessels, while the superficial layer of the optic nerve head is supplied by small branches originating from the central retinal artery. It maybe that an alteration in blood flow in the anterior optic nerve head can cause hypoxic injury, resulting in ganglion cell death.

Although the involved quadrants were different in the present study and previous studies, they align on the finding that migraine can result in focal decrease in cerebral blood flow, and partircularly in retinal circulation.

Regarding the significant difference of RNFL thickness in inferior and temporal quadrants between migraine group (MWA+MWoA) and the control group, it might be hypothesized that retinal infarctions due to occlusion of retinal arterybranches have a role in migraine. To confirm this, larger studies are required.

Interestingly, RNFL thickness measurement could be a useful technique through which to evaluate the severity and the evolution of migraine, and perhaps to study whether prophylactic treatment could reduce retinal abnormalities seen in migrainous patients. OCT-SD is a harmless exam that could be used in children and repeated for evaluation of headache progression.

The main limitation of our study is the small number of cases. However, the number of patients per group was comparable to those conducted in studies with adults.

In conclusion, the peripapillary RNFL was significantly thinner in children with migraine than in the healthy control subjects, particularly in the migrainous with aura. Our study suggests that in children, migraine leads to a thinning of the peripapillary RNFL thickness. Such thinning is thought to be related to a progressive loss of ganglion cells and axons caused by the chronic nature of headache disorders. Our results confirm these data, and suggest that this may happen due to pathogenesis of migraine, rather than in relation to the natural aging process.

Future studies could also identify whether appropriate prophylactic treatment which reduces the frequency of attacks and duration of the headache may prevent thinning the RNFL thickness in children with migraine.

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