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Original Article

USING OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY TO CORRELATE PERIPAPILLARY CAPILLARY DENSITY TO PAPILLEDEMA GRADE IN IDIOPATHIC INTRACRANIAL HYPERTENSION

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Abstract

Purpose: *Evaluation of the peripapillary microvascular density and neuronal changes in patients with idiopathic intracranial hypertension (IIH) in correlation with the degree of papilledema clinically at time of presentation.* ***Methods:*** *This case-control study included 112 eyes of 84 individuals. They were divided into IIH with papilledema group; 56 eyes of 28 patients and control group; 56 eyes of 56 healthy age and sex matched participants. Optical coherence tomography angiography (OCTA) to evaluate the Retinal nerve fiber layer (RNFL) and peripapillary capillary vessel density (CVD) was done with colored fundus photography for documentation of papilledema.* ***Results:*** *The difference in CVD and RNFL were statistically significant between both groups with lower vessel density and thicker RNFL in the IIH group. The thickness of the RNFL was correlated with the degree of papilledema unlike CVD.* ***Conclusion:*** *OCT-A revealed a reduction in the CVD, which could be caused by the thickening the RNFL due to swelling of the axons in the peripapillary area caused by papilledema. Overall, OCT-A has the ability to quantify CVD, identify areas of hypoperfusion, and spot early ischemic abnormalities in IIH patients before they develop optic nerve atrophy.*

Keywords: *IIH, peripapillary capillary vessel density, OCTA, Nerve fiber layer thickness*

1. Introduction

High intracranial pressure without a clear cause is the hallmark of idiopathic intracranial hypertension (IIH), formerly named pseudotumor cerebri or benign intracranial hypertension mostly affects obese females in the child bearing period [1]. Its incidence is around 0.5-2 individuals per 100,000. Recently, obesity is becoming more prevalent thus this percentage will continue to rise [2]. In 90% of the cases, papilledema and headache usually exist [3]. IIH is considered as visual threatening disease which varies in presentation. Patients complain from transient visual obscurations, double vision, and field affection, up to visual loss due to optic atrophy [4]. There are two main mechanisms for damage to the optic disc due to increased intracranial pressure; disruption of axonal transport in optic nerve head (ONH) and intraneuronal ischemia. High intracranial pressure is likely to disrupt the usual gradient between intra-

ocular and retrolaminar pressure, which then causes the pressure inside the optic nerve (ON) to increase. This causes axoplasmic flow to be disrupted, resulting in stasis and intra-axonal edoema. ON ischemia is a further significant mechanism where intra-axonal edoema and compression of tiny vessels happen when the pressure at the ONH is disturbed. Then, the optic nerve suffers intraneuronal ischemia injury as a result [5]. Patients with IIH may have altered ONH blood flow, according to earlier studies [6]. OCT-A can be used to assess the radial peripapillary plexus (RPC) which is the vascular bed at the level of the RNFL that provides quantitative information on the retinal microvasculature in addition to the detection of anomalies in ONH perfusion [7,8]. The majority of earlier studies on IIH used OCT to measure the thickness of the RNFL but neglected to measure the RPC. We postulate that data from OCT anatomical imaging and OCT-A CVD measurements could offer supplementary information that is useful for both pathogenesis and therapeutic management of papilledema.

2. Materials and Methods

This case control study evaluated fifty-six eyes of 28 patients compared to fifty-six eyes of 56 ages and sex matched healthy controls. The study applied the tenets of the Declaration of Helsinki and the research ethical committee approvedit. A comprehensive explanation of the study was given to the participants and they approved an informed written consent. All participants' names were hidden & were replaced by coding symbols to maintain privacy of the patients.

2.1. *Patients' selection*

IIH patients with papilledema and IIH according to modified Dandy criteria in the age group 18-48 years old were included in our study. Patients with papilledema due to any cause other than IIH, pediatric IIH or with any preexisting retinal or other optic nerve disease such as glaucoma were excluded. Also, those with any history of diabetes, hypertension, cardiac disease or any vascular co-morbidity, or on oral anticoagulant or had previous intraocular surgery were excluded. We also excluded high myopia or hypermetropia, media opacity obscuring optimal fundus assessment and severe cases of papilledema grade 4 and 5 not allowing good OCT angiography imaging. Participants were divided into two groups: Group 1 (IIH patients with papilledema): 56 eyes of 28 patients. Group 2 (healthy): 56 eyes of 56 age and sex matched control. Full medical history of all patients were obtained including age of onset, main complaints, history of any systemic diseases, previous surgeries or drug intake. The opening pressure on lumbar puncture, neuroimaging findings, and any therapy prescriptions, were all evaluated from the medical records. Eyes of all participants were assessed regarding their best-corrected visual acuity (BCVA) using Snellen's chart, anterior segment examination, intraocular pressure measurement (IOP) with Goldman applanation tonometry, detailed fundus evaluation by binocular indirect slit-lamp biomicroscopy. Colored fundus photography for documentation (Topcon "TRC 50 LX model Tokyo, Japan) was done. and finally OCT ONH using Optovue OCT to asses RNFL and OCTA of the peripapillary vessel density using AngioVue (Optovue Inc., Fremont, CA, USA) to assess CVD.

2.2. *Evaluation of OCTA scans*

Centered on the ONH, a 4.5*4.5 -mm rectangular examination was completed. The evaluation of RNFL and CVD was performed using the integrated Angio-Analytics software. The peripapillary region is described as a circular annulus

that is 1.0 mm wide and extends from the edge of the optic disc. The Bruch's Membrane Opening (BMO) is used to automatically determine the disc margin, and the cup and rim are both assessed inside the BMO level. The optic nerve head served as the center of a 3.45 mm-diameter circle along which RNFL readings were computed in a band 10 pixels wide. The temporal, nasal, superior and inferior quadrants, as well as the RNFL thickness, were measured. CVD is the proportion of the peripapillary region's surface area that is occupied by vessels. The software determined the overall peripapillary vascular density (wiVD) in the full 4.5*4.5 mm^2 scan. Additionally, the nasal, inferior, superior, and temporal quadrants' VD were assessed. Also, color maps were employed to display the vessel density.

3. Results

The age of the patients was from 19 to 46 years with a mean age of 33.19±8.60 years in the IIH group and from 19 to 48 years with a mean age of 32.71±8.39 years in the control group with no difference statistically. We had 27 females and one male in the patients' group compared to 54 females and 2 males in the control group with no statistical difference. The main presenting symptoms were headache in (100%) of the patients and blurring of vision was reported in (77.8%). Other symptoms like tinnitus and diplopia were reported in (22.2%). History of use oral contraceptive pills was reported in (OCP) (50%).

3.1. *Clinical data*

There was a statistically significant difference in BCVA mean value between both groups (P value <0.001). While the mean intracranial pressure (ICP) was 422.96 ± 155.47 mmHg. Clinical data are elaborated in tab. (1). Since we excluded advanced cases of papilledema, the grades of papilledema in the examined patients were variable up to grade 3 only, where grade 1 constituted 19 eyes (35.2%), grade 2 constituted 27 eyes. (50.0%) and grade 3 was found in 8 eyes (14.8%). The main lines of treatment varied between medical and surgical approaches. Oral carbonic anhydrase inhibitor was the most commonly used drug in 49 of patients (90.7%). Surgical intervention was done in the form of shunts in 33 patients (61.1%).

Table 1: Clinical data presentations in both groups

	Cases					Control					
	Mean	***SD***	***Median***	***Mini.***	***Max.***	***Mean***	***SD***	***Median***	***Min.***	***Max.***	***P value***
Age	33.19	8.60	34.00	20.00	46.00	32.71	8.39	36.00	19.00	49.00	0.756
BCVA	0.61	0.28	0.60	0.05	1.00	0.94	0.06	0.90	0.80	1.00	<0.001
IOP	13.31	1.55	13.00	10.00	17.00	13.54	1.20	14.00	12.00	16.00	0.468
ICP	422.96	155.47	390	200	700						

3.2. *Imaging*

3.2.1. Comparing CVD

There was a statistically significant variation in the inside disc VD, nasal and temporal peripapillary VD between both groups with the details are shown in tab. (3) (*p* value 0.004), (*p* value 0.006), (*p* value < 0.001) respectively and fig_s. (1, 2 & 3). There was a statistically significant negative correlation between the whole image VD and ICP (r= -0.285, *p* value 0.037). Correlating VD to duration of the diseases revealed a statistically significant negative correlation in the temporal quadrant (r= -0.445, *p* value <0.001). We found no correlation between CVD assessed by OCTA and grade of Papilledema (*p value* > 0.01).

Table 2: Analysis of vessel densities in different quadrants

OCTA –vessel density (%)	Cases					Control					
	Mean	SD	Median	Mini.	Max.	Mean	SD	Median	Min.	Max.	P value
whole image	50.57	3.43	51.60	41.80	56.50	52.13	1.53	52.00	48.00	55.00	0.058
inside disc	53.36	4.41	53.75	40.20	63.70	51.11	3.39	51.60	41.20	57.00	0.004
peripapillary	53.21	3.91	54.20	41.90	59.20	54.41	2.21	54.00	48.00	59.00	0.186
superior hemi	52.42	4.98	53.25	33.60	60.10	53.23	7.50	53.65	5.00	59.60	0.270
inferior hemi	53.77	3.93	54.60	42.30	59.40	54.49	2.19	54.60	50.00	59.00	0.605
superior	52.61	6.64	54.50	32.00	63.00	54.94	2.74	54.50	49.00	61.00	0.359
inferior	56.23	5.24	57.00	40.00	65.00	57.08	3.05	57.00	48.00	61.00	0.562
nasal	51.85	4.67	53.00	39.00	60.00	54.13	3.27	55.00	45.00	60.00	0.006
temporal	52.33	5.69	53.00	38.00	65.00	55.60	2.22	55.50	50.00	60.00	<0.001

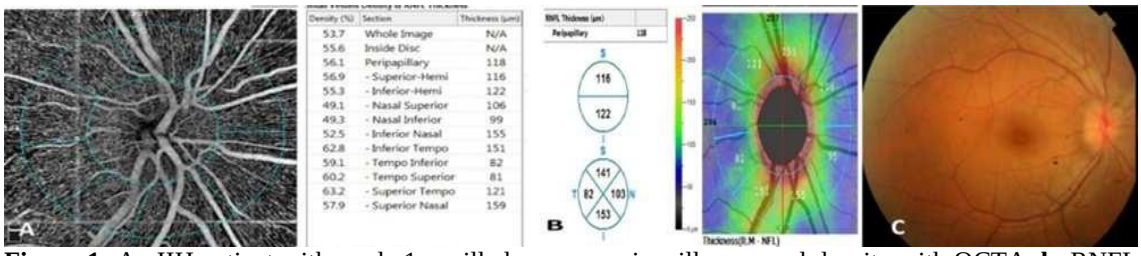

Figure 1: An IIH patient with grade 1 papilledema; **a.** peripapillary vessel density with OCTA, **b.** RNFL thickness with OCT, **c.** colored fundus photo of grade 1 papilledema.

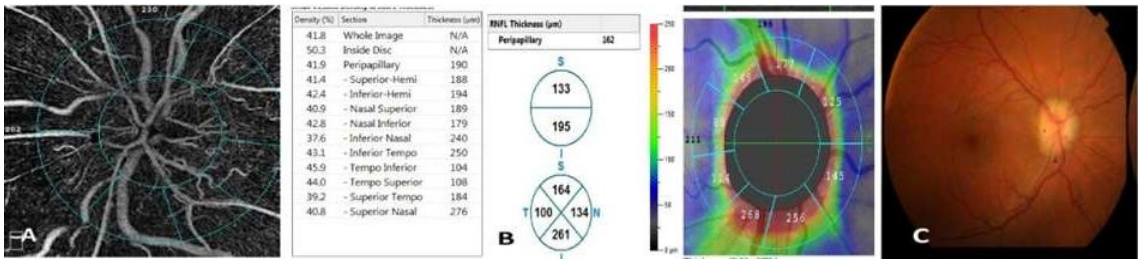

Figure 2: An IIH patient with grade 2 papilledema; **a.** peripapillary vessel density with OCTA, **b.** RNFL thickness with OCT (b), **c.** colored fundus photo of grade 2 papilledema.

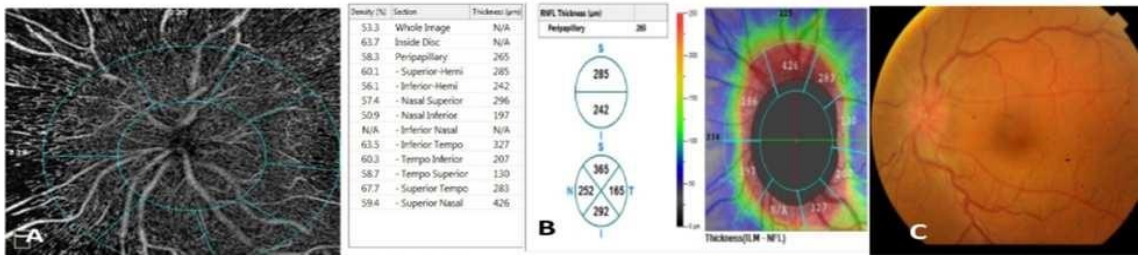

Figure 3: An IIH patient with grade 3 papilledema; **a.** peripapillary vessel density with OCTA, **b.** RNFL thickness with OCT, **c.** colored fundus photo of grade 3 papilledema (c)

3.2.2. Comparing RNFL thickness

The difference in RNFL thickness in all quadrants was significant between both groups statistically (superior, inferior, nasal and temporal) (*p* value <0.001, <0.001, <0.001, 0.002, respectively) as shown in tab. (3). There was a statistically significant positive correlation between OCT NFLT and grade of papilledema in superior, inferior, nasal and temporal quadrant. (r= 0.452, *P* <0.001), (r= 0.545, *p*<0.001), (r= 0.334, *p*= 0.013), (r= 0.358, *p*= 0.008) respectively. There was a statistically significant positive correlation between OCT NFLT and ICP in superior, nasal and temporal quadrant (r= 0.298, *p*= 0.029), (r= 0.307 *p*= 0.025), (r= 0.381, *p*= 0.004) respectively. Correlating RNFL to duration of the disease revealed a statistically significant positive correlation in the superior (r= 0.392, p = 0.003) and temporal (r= 0.286, *p*= 0.036) quadrants.

Table 3: Comparison between RNFL

OCT-RNFL (μ)	Cases					Control					
	Mean	*SD*	*Median*	*Mini.*	*Max.*	*Mean*	*SD*	*Median*	*Min.*	*Max0*	*P value*
Superior	170.91	85.54	156.50	12.00	512.00	128.42	13.11	127.00	100.00	160.00	<0.001
Inferior	201.53	61.85	189.00	121.00	424.00	128.90	13.44	126.50	110.00	160.00	<0.001
Nasal	149.46	74.30	139.50	38.00	537.00	85.58	7.20	85.00	75.00	104.00	<0.001
Temporal	97.78	41.18	83.00	46.00	260.00	76.12	7.05	75.00	65.00	90.00	0.002

4. Discussion

The actual pathogenesis of visual affection in papilledema in the context of IIH is uncertain. Ischemia with reduced blood supply to the ONH is one possible explanation. However, viewing papilledema as "neurovascular unit damage" expands the range of investigations available for early diagnosis, monitoring the severity, and its follow-up [9]. Along the RNFL, the RPCs constitute a unique capillary plexus. Because of the enormous energy demands imposed on the non-myelinated axons in the RNFL, it is extremely vulnerable to ischemia insults like papilledema. As a result, examining changes in RPCs and the RNFL can be utilized to evaluate the ONH perfusion abnormalities in IIH [10]. This study investigated the affection of RPC in IIH and correlated RPC density with the degree of papilledema in IIH to evaluate the ischemic effect in IIH and if OCTA can be used for early detection of optic disc damage and if it's correlated with the degree of papilledema. Using OCT-A slab, we studied the relationship between RPC and papilledema in patients with IIH and whether if there was a relation between the VD and the degree of papilledema. The VDs were measured throughout the whole image, inside the disc, the peripapillary zone; the superior, inferior, nasal, and temporal regions. These measurements were also compared to their analogues in the control group. The CVD evaluated using OCT-A in patients with papilledema secondary to IIH was found to be significantly less than those of the control group, particularly in the temporal and nasal areas and inside the disc. Peripapillary VD, on the other hand, was not found to be correlated with the Frisen papilledema grade. These findings are in agreement with previously published papers that showed a reduced CVD in IIH patients. "Fatma SelinKaya et al [11] in 2021 measured the thickness of the RNFL, the ganglion cell complex (GCC), and the CVD in the papilledema patients with IIH and found that they have an affection of the vasculature in the lower nasal region, where OCT-A was able to detect. Also, Tüntaş Bilen et al [10] investigated the CVD in IIH and its correlation to papilledema grade. They documented the finding of a significantly reduced CVD using OCTA in patients with papilledema secondary to IIH and in agreement with our study, the rate of affection of the CVD was not found to be correlated with the Frisen papilledema grade. We found a statistically significant negative correlation between the whole image VD and ICP. Also, CVD had statistically significant negative correlation in the temporal quadrant with the duration of the diseases. The reduced RPC vessel density in papilledema patients could be attributed to a number of factors. Patients with IIH have previously been found to have a low blood flow despite high cerebral blood volume. High cerebral vasculature resistance, impairment of cerebral blood flow autoregulation, or reduction in the vessels density related to brain edema can all lead to a reduced cerebral blood flow in IIH. Another explanation for the decrease in vessel density is that the ophthalmic artery and central retinal artery flow through the subarachnoid space and are impacted by changes in the ICP [11]. With higher CSF pressures, systolic flow in both arteries decreased. High flow resistance, axonal swelling of the ONH, and

focal vessels dilatation, all together were the roots of decreased flow. In addition, mechanical factors should be considered. When ICP rises, the axoplasmic flow stagnates, resulting in capillary network compression [11]. On the other hand, "Marie-Bénédicte Rougier" in (2018) [12] evaluated the change of the peripapillary VD in subjects with acute phase disc edema, including non arteritic ischemic optic neuritis (NAION), papillitis, and papilledema. Four patients (8 eyes) having NAION, six patients (12 eyes) having papillitis, and thirteen patients (25 eyes) with papilledema were examined as part of the investigation. The vessels on the optic disc were convoluted and dilated in papilledema, but there were no alterations in the peripapillary vascular architecture. So; OCT-A can be used as a reliable imaging tool that aids in the discrimination between the 3 types of ONH edema: ischemic, inflammatory and papilledema [12]. This current study found that the RNFL thickness was thickened in all localizations by OCT showing a statistically significant direct correlation with ICP. This is in agreement with "Shashi Ahuja's et al [13] findings, who also found that RNFL thickness increases in the inferior and superior peripapillary areaes and was more prevalent in severe degrees of papilledema. Again, Kiran Malhotra et al [14] evaluated the RNFL in IIH subjects with papilledema. According to their study, the RNFL thickness increases with papilledema secondary to IIH compared to normal values. According to our findings, vessel density measured by OCTA could be sensitive tool in quantifying the vessel density and identifying areas of non-perfusion. These findings are significant because they confirm the theory that papilledema optic neuropathy is caused by a relative ischemia condition, which over time could result in the peripapillary area and optic disc damage, leading to optic nerve atrophy and gliosis. The study is limited by the non-correlation of the functional examination such as pupillary reaction affection and visual field changes.

5. Conclusion

OCT-A showed a decrease in the peripapillary vascular density, which is a consequence to the papilledema-induced axons swelling in the peripapillary retina, which thickened the RNFL. All things considered, OCT-A can measure vascular density, highlight non-perfusion regions, and find early ischemia anomalies in IIH patients before they experience ocular atrophy and gliosis.

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