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Glaucomatous Versus Non-Glaucomatous Optic Disc Cupping

Hasnaa E. Salama, Tarek A. Mohsen, Eman M. EL-Hefney, Rania K. Farag.

Department of ophthalmology - Faculty of medicine - Mansoura University – Egypt

Corresponding author: Hasnaa E. Salama, Mansoura Ophthalmic Center, Faculty of Medicine, Mansoura University, Mansoura, Egypt. PO: 35516. Tel. 01282444838, Fax 002-050-2202064, E mail: hameto89@yahoo.com.

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Running Title: Glaucomatous Versus Non-Glaucomatous Optic Disc Cupping.

Abstract

Propose: Cupping of the optic nerve head is a classic sign of glaucoma; however non-glaucomatous optic neuropathies can cause changes of the optic nerve head as well. Currently, information from visual field (VF) examination by automated perimetry, optic nerve head pallor and visual acuity are used to aid in differentiating glaucomatous from non-glaucomatous optic nerve cupping. Optical coherence tomography (OCT) has been shown to have good reproducibility of retinal nerve fiber layer thickness (RNFL thickness) measures and monitoring glaucomatous disease progression.

Aim of work: The current study was conducted to differentiate between glaucomatous from non-glaucomatous optic disc cupping based on clinical and investigation methods.

Patients and Methods: This study included a total of 50 eyes with optic cupping; 32 eyes with glaucoma, 8 eyes with neurological disorders, 8 eyes with physiological cupping and only two eyes glaucoma suspects. All patients were subjected to ophthalmic examinations and investigations to assess causes of optic disc cupping.

Results: There was no significant difference between studied groups regarding cup to disc ratio. There was statistically significant difference between studied groups regarding ISNT rule (that normal eyes show a characteristic configuration for disc rim thickness of inferior ≥ superior ≥ nasal ≥ temporal), only 28.1% of eyes in glaucoma group followed the rule, compared with 50.0% in neurological disorders. All eyes with physiologic cupping or who were glaucoma suspect followed that rule. No visual field defects were detected in physiological cupping and glaucoma suspect eyes, although glaucomatous eyes showed visual field defects respecting the horizontal meridian in most of the studied eyes, while neurological disorders eyes respected the vertical meridian.

Conclusion: Visual field and OCT appeared to be a useful technology in evaluation non-glaucomatous optic disc cupping, as the pattern of RNFL loss was varied depending upon the etiology.

Keywords: Non-glaucomatous cupping, Optical coherence tomography, Retinal nerve fiber layer

INTRODUCTION

Optic disc cupping is commonly referred to as glaucoma; However glaucoma is not the only cause of optic disc excavation.[1] Previous studies showed that 20% of patients with non-glaucomatous optic disc changes were misdiagnosed as glaucoma.[2] Other causes than glaucoma that may cause optic disc cupping include physiological cupping, arteritic anterior ischemic optic neuropathy,[3, 4] non-arteritic anterior ischemic optic neuropathy,[3, 4] posterior ischemic optic neuropathy, increase intracranial tension, optic neuritis,[5] and Leber hereditary optic neuropathy. Clinical signs such as optic nerve head pallor can be used in differentiating glaucomatous from non-glaucomatous optic disc cupping; however clinical differentiation is sometimes difficult even for experienced observers;[6] so many investigations are used like optical coherence tomography, visual field testing and pachymetry for accurate diagnosis.

Optical coherence tomography is non- invasive rapidly obtained imaging tool that employs near infrared light to create cross sectional images of retina and optic nerve head, and also to analyze the optic nerve head, macula and retinal nerve fiber layers.[6, 7] Optical coherence tomography has been shown to have good reproducibility in RNFL thickness measures , suggesting that it may be useful clinical tool to monitor glaucomatous disease progression.[8]. Visual field testing also can be used to measure severity of visual loss in glaucomatous and non-glaucomatous optic nerve damage. Optic nerve examination usually reveals thinning of neuro retinal rim in patterns corresponding to visual field loss.[9]

Intra ocular pressure represents one of the important parameters in diagnosis of glaucoma, however it's not the only factor, it can be affected by central corneal thickness as thicker corneas resulted in a higher intra ocular pressure estimate, while thinner corneas resulted in lower estimate than actual value. So several imaging devices have been developed for accurate estimate like pachymetry.[10] However, there have not been many studies that give a protocol for assessment of cases with large optic disc cupping. That is why different investigative tests (such as OCT and automated perimetry) beside detailed clinical examination should be used to get the accurate final diagnosis.

So, the aim of this study was to differentiate between glaucomatous from non-glaucomatous optic disc cupping by different clinical and investigation methods.

PATIENTS AND METHODS

This was a cross sectional observational, analytical study that was conducted to evaluate glaucomatous versus non-glaucomatous optic disc cupping by clinical and investigation methods at Mansoura ophthalmology center at Mansoura University in Mansoura in Egypt. The study was conducted for a duration of 1 year in the period from Jan 2020 to Jan 2021.The study included patients with large optic disc cupping, of both sex and different age groups, with excluding of patients with spherical equivalent >±5 diopters, patients with hazy media causing poor OCT quality and patients with retinal pathology (i.e. diabetic retinopathy, cystoid macular edema, and central retinal vein occlusion). A written informed consent was obtained from all the participants before inclusion in the study.

Methods

After the study get the approval by the institutional review board (IRB), Faculty of Medicine, Mansoura University, code number MS. 48.10.341. All patients were subjected to history taking inform of demographic data that included Full general and ophthalmic history (age, gender, history of previous intraocular surgery, neurologic, metabolic, or systemic diseases). Also, they were subjected to full ophthalmic examination that included visual acuity (VA) assessment that was done by Landolt's VA chart and then transformed for statistical analysis to Decimal VA then to LogMAR VA, patient's refractive error assessment by Autorefractometer by Topcon RM-800 autorefractometer, anterior segment examination by the slit lamp biomicroscopy (Haag Streit BP 900) (Haag-Streit, Koeniz, Switzerland), posterior segment examination by indirect ophthalmoscope or slit lamp biomicroscopy with auxiliary contact lens, central corneal thickness measurement by ultrasound pachymetry, intraocular pressure measurement by Goldman applanation tonometer, optical coherence tomography (OCT) by Spectral domain OCT 2000 to assess optic nerve cup disc ratio and the patients were also subjected to visual field tests by automated perimetry Zeiss Humphrey field analyzer that can detect dysfunction in central and peripheral vision which may be caused by various medical conditions such as glaucoma, brain tumors or other neurological disorders.

Statistical Analysis

Data were fed to the computer and analyzed using IBM SPSS Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp. Qualitative data were described using number and percent. Quantitative data were described using median (minimum and maximum) for non-parametric data and mean, standard deviation for parametric data after testing normality using Kolmogorov-Smirnov test. Significance of the obtained results was judged at the (0.05) level. For qualitative data; Monte Carlo test as correction for Chi-Square test when more than 25% of cells have count less

than 5 in tables (>2*2) was used. One Way ANOVA test was used to compare more than 2 independent groups with Post Hoc Tukey test. For non-parametric data; Kruskal Wallis test was used to compare more than 2 independent groups.

RESULTS

This was cross sectional observational study included 50 eyes of 32 patients with large optic disc cup divided into 4 groups according to clinical finding, Optical Coherence Tomography and Visual field parameters. The mean age of the studied cases was (43.70±17.79) years ranging from 11 to 70 years, 58% male, 42%female and medical history of 100% of cases was free. (Table 1)

Table (1): Demographic characteristics of the studied cases.

	Total number =32	**%**
Age/years		
mean±SD (range)	43.70±17.79 (11-70)	
Gender		
Male	19	58.0
Female	13	42.0
Medical history		
Free	32	100

Regarding visual, refractive data and anterior segment examination characters among studied eyes; the mean visual acuity was (0.60±0.33),36% myopic, 64% hypermetropic and mean best corrected visual acuity assessed by logMAR was (0.41±0.32). Regarding anterior segment examination of studied eyes, 54% had clear lens and 46% nuclear sclerosis. Mean central corneal thickness was (540.98±32.29). Regarding **fundus examination among studied eyes;** the mean cup/disc ratio was (0.628±0.162), deep cup was found among 68% of the studied eyes, 60% nasal shift of blood vessels and 16% pallor exceeding cupping (Table 2).

Table (2): Visual, refractive data, anterior segment and fundus examination characters among studied eyes

	Total number =50	%
Visual Acuity (LogMAR)		
median (range)	0.6(0.17-1.08)	
mean±SD	0.60±0.33	
Refraction		
Myopic	18	36.0
Hypermetropia	32	64.0
Best Corrected Visual Acuity		
(logMAR)	0.39(0.0-1.0)	
median (range)	0.41±0.32	
mean±SD		
Anterior segment		
Clear lens	27	54.0
Nuclear sclerosis	23	46.0
Central Corneal Thickness (µm)		
median (range)	531(490-639)	
mean±SD	540.98±32.29	
Cup/disc ratio		
Mean±SD (range)	0.628±0.162(0.40-0.90)	
Deep Cup		
-ve	16	32.0
+ve	34	68.0
Nasal shift of Blood Vessels		
-VE	20	40.0
+VE	30	60.0
Pallor Exceeding Cupping		
-ve	42	84.0
+ve	8	16.0

Optical Coherence Tomography (OCT) measurements among studied eyes showed that, 46% of the studied eyes followed ISNT rule, 16% of eyes had mild thinning and 40% showed severe thinning in the superior RNFL thickness, 16% of eyes had mild thinning and 42% showed severe thinning in the inferior RNFL thickness, 20% of eyes had mild thinning and 20% showed severe thinning in nasal RNFL thickness, 14% of eyes had mild thinning and 18% showed severe thinning in temporal RNFL thickness and the mean OCT measured cup disc ratio was (0.583±0.166) (Table 3, Figure 1).

Table (3): Optical Coherence Tomography (OCT) measurements among studied eyes

OCT	N=50	%
Follow ISNT rule		
-ve	27	54.0
+ve	23	46.0
RNFL thickness (superior)		
Average	22	44.0
Mild thinning	8	16.0
Severe thinning	20	40.0
RNFL thickness (inferior)		
Average	21	42.0
Mild thinning	8	16.0
Severe thinning	21	42.0
RNFL thickness (nasal)		
Average	30	60.0
Mild thinning	10	20.0
Severe thinning	10	20.0
RNFL thickness (temporal)		
Average	34	68.0
Mild thinning	7	14.0
Severe thinning	9	18.0
OCT Cup/Disc ratio		
Median (Range)	0.575(0.32-0.96)	
Mean±SD	0.583±0.166	

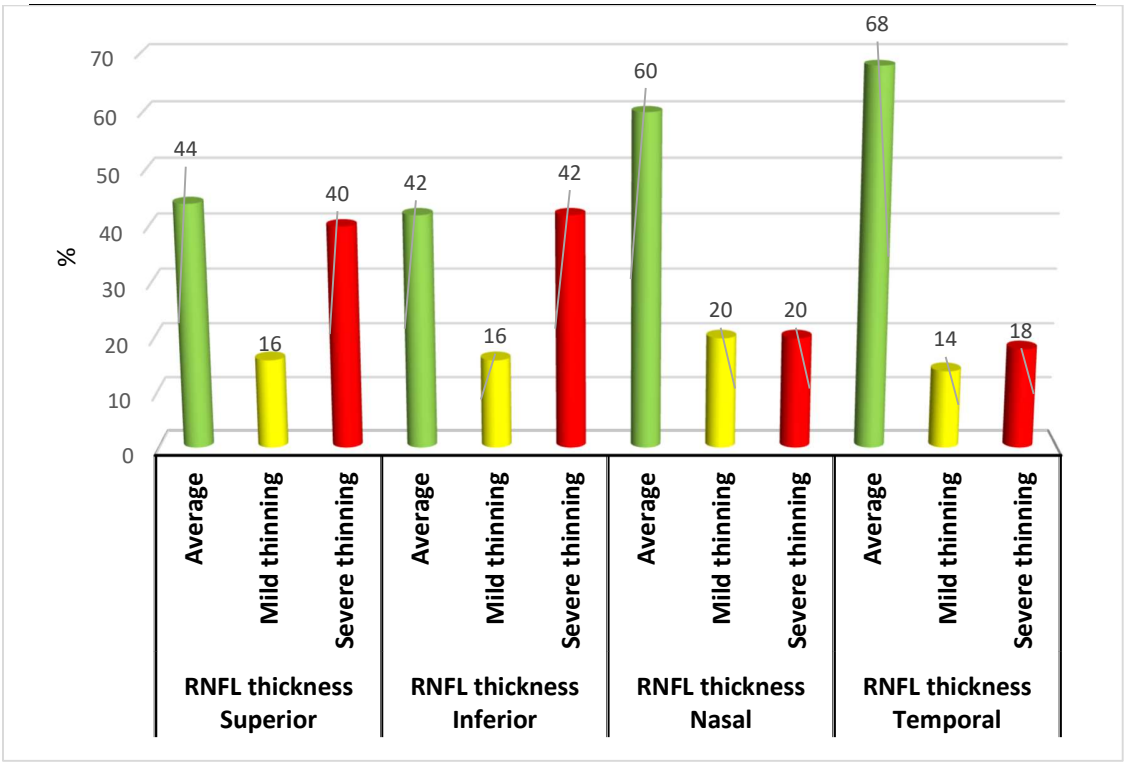

Figure (1) OCT RNFL thickness among studied eyes.

Visual field changes of the studied eyes (estimated by automated perimetry) showed that 52% studied eyes were outside normal limits and 8% borderline regarding glaucoma hemifield test. The mean deviation (MD) was -4.85 ± 3.0 and pattern standard deviation (PSD) was 5.51±5.03. Regarding visual field changes among studied eyes; 32% were within normal VF, 6% were with generalized loss of sensitivity, 4% with nasal step, 10% with enlarged blind spot, 14% with upper paracentral scotoma, 6% with lower paracentral scotoma, 12% with upper arcuate scotoma, 14% with lower arcuate scotoma, 12% with homonymous hemianopia, 4% with Bl temporal hemianopia and 8% with constricted VF (Table 4).

Table (4): Visual field changes of the studied eyes (estimated by automated perimetry)

Visual field	N=50	%
Glaucoma Hemifield Test (GHT)		
Within normal limit	20	40.0
Borderline	4	8.0
Outside normal limits	26	52.0
Mean Deviation (MD)	-4.85±3.0	
Pattern Standard Deviation (PSD)		
Mean±SD	5.51±5.03	
within normal Visual Field		
-ve	34	68.0
+ve	16	32.0
Generalized loss of sensitivity		
-ve	47	94.0
+ve	3	6.0
Nasal step		
-ve	48	96.0
+ve	2	4.0
Enlarged blind spot		
-ve	45	90.0
+ve	5	10.0
Central scotoma		
-ve	50	100.0
+ve	0	0.0
Upper para central scotoma		
-ve	43	86.0
+ve	7	14.0
Lower para central scotoma		
-ve	47	94.0
+ve	3	6.0
Upper arcuate scotoma		
-ve	44	88.0
+ve	6	12.0
Lower arcuate scotoma		
-ve	43	86.0
+ve	7	14.0
Homonymous Hemianopia		
-ve	44	88.0
+ve	6	12.0
Bi temporal Hemianopia		
-ve	48	96.0
+ve	2	4.0
Constricted Visual Field		
-ve	46	92.0
+ve	4	8.0

The studied eyes were divided into four groups as 16% physiological cupping (8 eyes), 4% glaucoma suspect (2 eyes), 64% glaucoma (32 eyes) and 16% neurological disorders (8 eyes). (Figure 2)

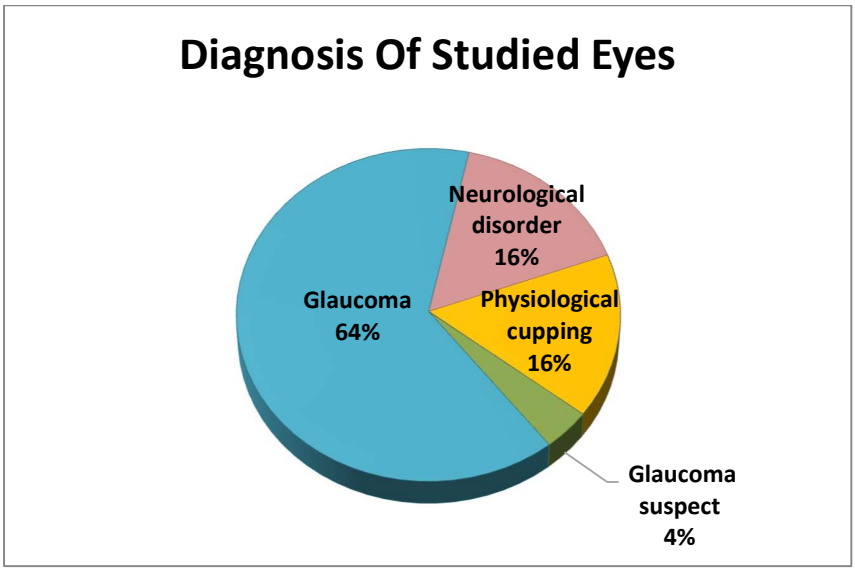

Figure (2) Diagnosis of studied eyes.

There was no statistically significant difference between the studied groups regarding gender, visual acuity, refraction, anterior segment, and central corneal thickness. Regarding association between intraocular pressure and diagnosis of studied eyes, no increase in intraocular pressure was found in Physiological cupping and neurological disorders eyes, with significant increase in both Glaucoma and Glaucoma suspect eyes more evident in glaucomatous eyes (Table 5).

Table (5): Demographic, visual data and anterior segment examination in relation to diagnosis of studied eyes

	Physiological cupping N=8 (16%)	Glaucoma suspect N=2 (4%)	Glaucoma N=32 (64%)	neurological disorders N=8 (16%)	Test of significance
Age/years					F=1.59
mean±SD	45.71±12.98	19.0±0.0	45.69±18.91	40.56±15.62	P=0.203
Gender N (%)					
Male	5(62.5%)	0(0.0%)	19(59.4%)	5(62.5%)	MC
Female	3(37.5%)	2(100%)	13(40.6%)	3(37.5%)	P=0.344
Visual acuity					F=2.46
mean±SD	0.51±0.31	0.30±0.0	0.57±0.34	0.82±0.22	P=0.074
Refraction N (%)					
Myopic	2(25.0%)	2(100%)	12(37.5%)	2(25.0%)	MC
Hypermetropia	6(75.0%)	0(0.0%)	20(62.5%)	6(75.0%)	P=0.168
BCVA					F=3.89
mean±SD	0.36±0.38	0.0±0.0	0.37±0.31	0.68±0.22	P=0.015*
Anterior segment					
Clear lens	5(62.5%)	2(100.0%)	16(50.0%)	4(50.0%)	MC
Nuclear sclerosis	3(37.5%)	0(0.0%)	16(50.0%)	4(50.0%)	P=0.614
Intra Ocular Pressure (mm /Hg)					F=20.59
mean±SD	16.51±0.84	21.3±0.0	27.86±4.29	19.40±5.0	P=0.001*
Central Corneal Thickness (µm)					F=0.383
mean±SD	538.29±12.17	525.5±3.5	544.31±37.78	534.67±24.28	P=0.766

F: One Way ANOVA test, MC: Monte Carlo test *statistically significant if p<0.05

There was no statistically significant difference between studied groups regarding mean cup/disc ratio but There was statistically significant difference among studied eyes regarding deep cup, nasal shift of blood vessels and pallor exceeding cupping with the highest frequency of deep cup was found in eyes with glaucoma and glaucoma suspect. Nasal shift of blood vessels was found among 93.8% of the eyes with glaucoma. Pallor exceeding cupping was detected among 100% of the eyes with neurological disorders. (Table 6)

Table (6): Association between fundus examination results and diagnosis of the studied eyes.

Fundus examination	**Physiological cupping N=8 (16%)**	**Glaucoma suspect N=2 (4%)**	**Glaucoma N=32 (64%)**	**Neurological disorders N=8 (16%)**	**Test of significance**
Cup/ Disc ratio					
median (range)	**0.6(0.5-0.7)**	**0.5(0.4-0.6)**	**0.65(0.4-0.9)**	**0.5(0.4-0.9)**	**KW**
Mean±SD	**0.600±0.057**	**0.40±0.0**	**0.659±0.158**	**0.589±0.203**	**P=0.23**
Deep cup N (%)					
-ve	8(100%)	0(0.0%)	0(0.0%)	8(100%)	MC
+ve	0(0.0%)	2(100%)	32(100%)	0(0.0%)	P<0.001*
Nasal shift of Blood Vessels N (%)					
-VE	8(100%)	2(100%)	2(6.2%)	8(100%)	MC
+VE	0(0.0%)	0(0.0%)	30(93.8%)	0(0.0%)	P<0.001*
Pallor exceeding cupping N (%)					
-ve	8(100%)	2(100%)	32(100%)	0(0.0%)	MC
+ve	0(0.0%)	0(0.0%)	0(0.0%)	8(100%)	P<0.001*

KW: Kruskal Wallis test, MC: Monte Carlo test *statistically significant if p<0.05

Regarding ISNT rule, there was statistically significant difference between glaucomatous and non-glaucomatous eyes, in glaucoma (28.1%) follow ISNT rule, neurological disorders (50.0%) follow ISNT rule and 100% in Physiologic cupping and Glaucoma suspect follow ISNT rule. Regarding association between peripapillary RNFL thickness and diagnosis of studied eyes, no thinning was found in physiological cupping with significant changes in both glaucomatous, neurological disorders and glaucoma suspect eyes as thinning in glaucomatous eyes more marked in (superior-inferior) quadrant but in neurological disorders more in (nasal –temporal). (Table 7)

Table (7): Association Between Optical Coherence Tomography (OCT) measurement and diagnosis of studied eyes

OCT	Physiological cupping N=8 (16%)	Glaucoma suspect N=2 (4%)	Glaucoma N=32 (64%)	neurological disorders N=8 (16%)	Test of significance
Follow ISNT rule					
-ve	0(0.0%)	0(0.0%)	23(71.9%)	4(50.0%)	MC
+ve	8(100%)	2(100%)	9(28.1%)	4(50.0%)	P=0.002*
RNFL thickness (superior)					
Average	8(100%)	0(0.0%)	13(40.6%)	1(12.5%)	MC
Mild thinning	0(0.0%)	2(100%)	3(9.4%)	3(37.5%)	P=0.02*
Severe thinning	0(0.0%)	0(0.0%)	16(50.0%)	4(50.0%)	
RNFL thickness (inferior)					
Average	8(100%)	2(100%)	10(31.2%)	1(12.5%)	MC
Mild thinning	0(0.0%)	0(0.0%)	5(15.6%)	3(37.5%)	P=0.005*
Severe thinning	0(0.0%)	0(0.0%)	17(53.1%)	4(50.0%)	
RNFL thickness (nasal)					
Average	8(100%)	2(100%)	19(59.4%)	1(12.5%)	MC
Mild thinning	0(0.0%)	0(0.0%)	8(25.0%)	2(25.0%)	P=0.024*
Severe thinning	0(0.0%)	0(0.0%)	5(15.6%)	5(62.5%)	
RNFL thickness (temporal)					
Average	8(100%)	2(100%)	22(68.8%)	2(25.0%)	MC
Mild thinning	0(0.0%)	0(0.0%)	6(18.8%)	1(12.5%)	P=0.122
Severe thinning	0(0.0%)	0(0.0%)	4(12.5%)	5 (62.5%)	

KW: Kruskal Wallis test, MC: Monte Carlo test *statistically significant if $p<0.05$

Regarding glaucoma hemifield test (GHT), it was within normal in both (physiological cupping-glaucoma suspect) with significant changes in both (glaucoma-neurological disorders), more marked in neurological disorders as all eyes were outside normal limits. Regarding mean deviation (MD), there was within normal parameters in both Physiological cupping and Glaucoma suspect eyes, with significant changes in both glaucoma and neurological disorders more marked in neurological disorders. No visual field defects detected in Physiological cupping and Glaucoma suspect eyes, although glaucomatous eyes showed visual field defects respecting horizontal meridian in most of eyes, while neurological disorders eyes respected vertical meridian (Table 8).

Table (8): Association between visual field finding and diagnosis of studied eyes

visual field	Physiological cupping N=8 (16%)	Glaucoma suspect N=2 (4%)	Glaucoma N=32 (64%)	neurological disorders N=8 (16%)	Test of significance
Glaucoma Hemifield Test (GHT)					
Within normal limit	8(100%)	2(100%)	10(31.2%)	0(0.0%)	MC
Borderline	0(0.0%)	0(0.0%)	4(12.5%)	0(0.0%)	P=0.003*
Outside normal limits	0(0.0%)	0(0.0%)	18(56.2%)	8(100%)	
Mean Deviation (MD)					KW
mean±SD	-0.18±1.91	-1.98±0.50	-5.67±2.1	-8.4±2	P=0.057
Pattern Standard Deviation (PSD)					KW
mean±SD	1.62±0.355	1.79±0.19	4.31±3.52	13.63±3.18	P<0.001*
within normal Visual Field					
-ve	0(0.0%)	0(0.0%)	25(78.1%)	8(100%)	MC
+ve	8(100%)	2(100%)	7(21.9%)	0(0.0%)	P<0.001*
Generalized loss of sensitivity					
-ve	8(100%)	2(100%)	29(90.6%)	8(100%)	MC
+ve	0(0.0%)	0(0.0%)	3(9.4%)	0(0.0%)	P=0.616
Nasal step					
-ve	8(100%)	2(100%)	30(93.8%)	8(100%)	MC
+ve	0(0.0%)	0(0.0%)	2(6.2%)	0(0.0%)	P=0.760
Enlarged blind spot					
-ve	8(100%)	2(100%)	27(84.4%)	8(100%)	MC
+ve	0(0.0%)	0(0.0%)	5(15.6%)	0(0.0%)	P=0.652
Central scotoma					
-ve	8(100%)	2(100%)	32(100%)	8(100%)	MC
+ve	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	P=0.199
Upper para central scotoma					
-ve	8(100%)	2(100%)	25(78.1%)	8(100%)	MC
+ve	0(0.0%)	0(0.0%)	7(21.9%)	0(0.0%)	P=0.205
Lower para central scotoma					
-ve	8(100%)	2(100%)	29(90.6%)	8(100%)	MC
+ve	0(0.0%)	0(0.0%)	3(9.4%)	0(0.0%)	P=0.616
Upper arcuate scotoma					
-ve	8(100%)	2(100%)	26(81.2%)	8(100%)	MC
+ve	0(0.0%)	0(0.0%)	6(18.8%)	0(0.0%)	P=0.280
Lower arcuate scotoma					
-ve	8(100%)	2(100%)	25(78.1%)	8(100%)	MC
+ve	0(0.0%)	0(0.0%)	7(21.9%)	0(0.0%)	P=0.205
Homonymous Hemianopia (H.H)					
-ve	8(100%)	2(100%)	32(100%)	2(25.0%)	MC
+ve	0(0.0%)	0(0.0%)	0(0.0%)	6(75.0%)	P<0.001*
Bi temporal Hemianopia					
-ve	8(100%)	2(100%)	32(100%)	6(75.0%)	MC
+ve	0(0.0%)	0(0.0%)	0(0.0%)	2(25.0%)	P=0.023*
Constricted Visual Field					
-ve	8(100%)	2(100%)	28(87.5%)	8(100%)	MC
+ve	0(0.0%)	0(0.0%)	4(12.5%)	0(0.0%)	P=0.485

KW: Kruskal Wallis test, MC: Monte Carlo test *statistically significant if p<0.05

DISCUSSION

Cupping of the optic nerve head is a classic sign of glaucoma, however non-glaucomatous optic neuropathies can cause changes of the optic nerve head as well.[11] Currently, information from perimetry, optic nerve head pallor and visual acuity are used to aid in differentiating glaucomatous from non-glaucomatous optic nerve cupping.[5, 12] Optical coherence tomography (OCT) has been shown to have good reproducibility of RNFL thickness measures and monitoring glaucomatous disease progression.[8] More recently OCT has been applied to evaluate eye diseases associated with neuro-ophthalmic conditions.[3] It can be used to track RNFL loss over time and can be correlated with visual dysfunction.[13] The current study was conducted at Mansoura University Ophthalmology Center to differentiate between glaucomatous from non-glaucomatous optic disc cupping based on clinical and investigation methods. This study included a total of 50 subjects with optic cupping; most of them were due to glaucoma (32 cases – 64%), followed by neurological disorders (8 patients – 16%), physiological cupping (8 subjects. – 16%) and only two patients were glaucoma suspects (4%).

In the present study, the mean age of the included cases was 45.69 years in the glaucoma group, compared to 40.56 and 45.71 years in the neurological and physiological cupping groups. In addition, the glaucoma suspect group had a mean age of 19 years. No significant difference was detected between the glaucomatous and non-glaucomatous cases regarding age ($p = 0.203$). In the current study, the mean best corrected visual acuity showed significant difference between the study groups ($p = 0.015$), as it was 0.37 in glaucoma group, compared to 0.68 and 0.36 in the neurological and physiological cupping groups. In addition, the glaucoma suspect group had 0.0. In the present study, intraocular pressure (IOP) showed a significant increase in the glaucomatous group, when compared to the neurological or physiological groups. This is in accordance with Aboobakar et al., 2016[14] who reported that normal IOP is a consistent finding in patients with non-glaucomatous optic cupping. However, Fard et al., 2019[15] reported comparable IOP findings between the two groups. This difference may be related to the large number of their eyes as the study of Fard et al., 2019[15] included 31 eyes of 31 patients with severe glaucoma, 33 eyes of 19 patients with non-glaucomatous cupping and 29 healthy controls eyes were also enrolled.

The current study showed no significant difference between glaucomatous and non-glaucomatous groups regarding cup to disc ratio ($p = 0.23$), which had a mean value of 0.65 in the glaucomatous group compared to 0.6, 0.5 and 0.5 in the physiological, neurological and glaucoma suspect groups respectively. In the same context, Gupta et al., 2011[5] reported that cup to disc ratio had mean values of 0.56 and 0.7 in the non-glaucomatous and glaucomatous groups respectively, with no significant difference between the two groups. In the current study, all glaucomatous eyes had a deep cup, while all non-glaucomatous subjects showed no deepening of their cups. This coincides with Fard et al., 2019[15] who reported that cupping is more profound in eyes with glaucoma compared to non-glaucomatous eyes. Shallow form of cupping is usually seen in non-glaucomatous optic neuropathies.[16]

In the present study,93%of glaucomatous eyes had nasal shift of blood vessels, while all non-glaucomatous eyes showed no shifting of their blood vessels. A significant difference was noted between the study groups ($p < 0.001$). This was in agree with Sawada et al., 2021[17] who showed that in eyes with glaucoma, the position of the central retinal vessel (CRV) on the optic nerve head (ONH) was more nasally angled than in normal eyes. In addition, eyes with worse glaucomatous VF defects exhibited significantly more nasal displacement of the CRV on the ONH. Consistent with results which were reported in previous two studies [18, 19]. Other study showed that vascular pattern seems to vary significantly between eyes with large physiological cupping and those with normal eyes.[20]

In the present study, pallor exceeding cupping was detected in all neurological eyes while it was absent in all glaucomatous eyes. A significant difference was noted between the study groups ($p < 0.001$).

Zhang et al., 2014[1] reported that the rim color is extremely important to differentiate between glaucomatous and non-glaucomatous causes of cupping. This was in agree with the

recent study when they reported that the rim of non-glaucomatous cupping often exhibits pallor. However, differentiating between non glaucomatous optic disc cupping (NGODC) and glaucomatous optic disc cupping (GODC) according to rim color is very difficult in end-stage glaucoma when the C/D ratio is ~1.0. Moreover, other authors[15] reported that non-glaucomatous eyes with cupping have greater degrees of neuro-retinal rim (NRR) pallor.

In the present study, there was statistically significant difference between glaucomatous and non-glaucomatous eyes regarding ISNT rule, only (28.1%) eyes in glaucoma group followed the ISNT rule compared to (50.0%) in neurological disorders. All eyes with Physiologic cupping or who were Glaucoma suspect followed the ISNT rule. This coincides with Sihota et al., 2008 and Harizman et al., 2006 as both published that ISNT rule has been shown to be not followed in adult patients with glaucoma compared with patients without glaucoma, and concluded that the ISNT rule is useful in differentiating normal from glaucomatous eye, as violation of the rule raises the suspicion of glaucoma.[21, 22]

On the contrary Lopes et al., 2014[20] found that a higher percentage of eyes with violation of the ISNT rule in large physiological cupping group in comparison with normal eyes. This may be explained by their eyes not followed clinically, as large physiological cupping eyes with violation of the ISNT rule may have been more likely to be followed clinically for possible glaucoma than those with large physiological cupping but no other features. Chan et al., 2013[23] reported high sensitivity and specificity values for the ISNT rule and its variants, they found a lower specificity in cases of large disc areas, as no single algorithm had a good combination of sensitivity and specificity. Therefore, although the ISNT rule has been largely applied to differentiate glaucomatous from normal cupped healthy eyes, it doesn't seem to be a good diagnostic parameter to use while dealing with eyes with large cups associated with large discs.

In the current study, regarding association between peripapillary RNFL thickness and diagnosis of studied eyes, no thinning was found in Physiological cupping with significant changes in both glaucomatous, neurological disorder and glaucoma suspect eyes as thinning in glaucomatous eyes more marked in(superior-inferior) quadrant but in neurological disorders more in (nasal -temporal). This coincides with study by Gupta et al., 2011[5] whom reported that the nasal and temporal RNFL thickness were lower in patients with non-glaucomatous optic nerve cupping compared to those with glaucomatous cupping and the RNFL loss in non-glaucomatous optic nerve cupping is not typically in the superior and inferior quadrants, as reported in glaucoma. Cases with physiological cupping showed normal RNFL thickness in all quadrants.

In this study, regarding mean deviation (MD), there were within normal parameters in both Physiological cupping and Glaucoma suspect eyes, with significant changes in both glaucoma and neurological disorder more marked in neurological disorder. These results agrees with the results of the study done by Dias et al., 2017[24] who showed that neuroophthalmological conditions had worse mean deviation values than those with glaucoma when comparing VF status between groups. However, Hata et al., 2014[25] showed that there was no significant difference in the MD between the compressive optic neuropathy (CON) and glaucoma groups ($p= 0.38$), but both groups had a significantly poorer MD than the healthy group ($p< 0.001$). This may be due to poor fixation of patients could impair the reliability of visual field testing as some CON and glaucoma patients had poor visual acuity.

The present study showed no visual field defects detected in Physiological cupping and Glaucoma suspect eyes, although glaucomatous eyes showed visual field defects respecting horizontal median in most of eyes, while neurological disorders eyes respected the vertical median. This was also confirmed by Gupta et al., 2021[12] who reported that glaucomatous field defects typically respect the horizontal meridian ,this may be owed to the arrangement of the retinal nerve fibers of the superior and inferior hemisphere meeting at the horizontal raphe. The resultant visual field defects in glaucoma are classically manifest as Bjerrum's scotoma or an arcuate scotoma. Visual field defects due to neurological compressive optic neuropathy do not respect the horizontal meridian and may be oriented vertically such as seen in hemianopia or quadrantanopia.

Conclusion

Visual field by automated perimetry and OCT appear to be a useful technology in evaluation non-glaucomatous optic disc cupping, as the pattern of RNFL loss was varied depending upon the etiology. There is a role for neuroimaging in evaluation of non-glaucomatous optic nerve cupping.

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DATA AVAILABILITY

All data are included in this article.

Corresponding author

Correspondence to: Hasnaa E. Salama

Email: hameto89@yahoo.com

Affiliations

Hasnaa E. Salama, Mansoura Ophthalmic Center, Faculty of Medicine, Mansoura University, Mansoura, Egypt.

Ethics declarations

Conflict of interest

Hasnaa E. Salama, Tarek A. Mohsen, Eman M. EL-Hefney, Rania K. Farag. all authors have no conflicts of interest that are directly relevant to the content of this review.

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