Med. J. Cairo Univ., Vol. 87, No. 1, March: 787-795, 2019
www.medicaljournalofcairouniversity.net

Correlation between Structural and Functional Changes in Glaucoma Patients Using Optical Coherence Tomography and Pattern Electroretinogram

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Abstract

Background: To study the correlation between peripapillary retinal nerve fiber layer (RNFL) thickness measured with Optical Coherence Tomography (OCT) and pattern electroretinogram (pERG) parameters in primary open-angle glaucoma (POAG) patients.

Aim of Study: To study the correlation between peripapillary RNFL thickness measured with OCT and pERG parameters in POAG patients.

Patients and Methods: Fifty eyes of 50 patients diagnosed with POAG and 15 eyes of 15 normal subjects as control group, were enrolled in a prospective comparative study. The eyes in the POAG group were further subdivided into mild, moderate, and severe subgroups. All eyes had visual field testing using 24-2 Humphery standard automated perimetry, peripapillary RNFL average thickness using the 3.4mm circular scan of the Heidelberg OCT spectralis and pERG using CSO RetiMax device in accordance with the International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines.

Results: There were significant differences in the visual field mean deviation (VF MD), peripapillary RNFL average thickness & some pERG measured parameters (N95 latency & P50-N95 latency) between normal and POAG eyes as were as among the three subgroups of POAG. Significant correlation was found between peripapillary RNFL average thickness and N95 amplitude (p<0.001), P50-N95 amplitude (p=0.002), N95 latency (p=0.034) & P50-N95 latency (p=0.045). We found significant correlation between peripapillary RNFL average thickness and N95 amplitude (p=0.001), P50-N95 amplitude (p=0.017) in POAG patients.

Conclusion: Peripapillary RNFL average thickness is significantly correlated with pERG N95 amplitude & P50-N95 amplitude. In combination with OCT, pERG can be used to objectively assess functional loss in glaucoma.

Key Words: *pERG – RNFL – OCT – POAG.*

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Introduction

PRIMARY open angle glaucoma is a major health problem. Being asymptomatic disease, it is usually discovered in its advanced stages. Early diagnosis of the disease depends mainly on the clinical suspicion of the ophthalmologist [1]. The current trend of diagnosis of primary open angle glaucoma includes the characteristic optic disc changes and the characteristic visual field changes [2]. Visual field is a commonly applied test in diagnosis of glaucoma. However, visual field testing as subjective, non-user friendly, affected by media opacities, and less sensitive for detecting early damage (it reveals glaucomatous defects only when 30 to 40% of the fibers have already been lost) [3]. Nowadays, optical coherence tomography for optic nerve head and retinal nerve fiber layer is widely accepted as a diagnostic tool of structural damage in glaucoma. It measures quantitatively the RNFL thickness in the peripapillary & macular regions [4]. Both macular and RNFL thickness as measured by OCT are significantly affected in glaucoma [5]. Macular ganglion cell layer and inner plexiform layer (mGCIPL) thickness is used in follow-up of glaucoma patients and their response to treatment whether medical or surgical [6].

The pattern electroretinogram (pERG) is an objective measurement of retinal response to a contrast reversing pattern, usually a black and white checkerboard. Pattern electroretinogram (pERG) changes reflect the electrical activity of retinal ganglion cells (RGCs) and it has been widely used to detect the loss of function of RGCs in glaucoma [7,8]. Cross-sectional studies have shown that pERG is frequently altered in patients with early glaucoma in comparison to normal controls [9]. Abnormal pERG responses were recorded in approximately 71% of glaucomatous eyes that had no field defect [10]. Forte et al., (2010) concluded that pERG abnormalities in eyes with ocular hypertension (OHT) or glaucoma suspect could suggest an early functional damage of viable retinal ganglion cells even in the presence of normal RNFL [11].

Patients and Methods

Our study is a comparative cross-sectional study. The study participants were recruited from patients attending outpatient clinic at Tanta University Hospitals. The recruitment started in April 2017. The study involved 65 eyes (50 eyes of glaucoma patients at different stages of glaucoma including mild, moderate and severe glaucoma with 15 eyes of normal age-matched control).

Inclusion criteria: For glaucoma patients; adult onset, glaucomatous optic nerve damage, an open anterior chamber angle, characteristic visual field loss, absence of signs of secondary glaucoma or a non-glaucomatous cause for the optic neuropathy & elevated intraocular pressure (IOP) [2]. The normal control group included individuals with normal optic disc, open anterior chamber angle and normal visual field.

The following were excluded from our study: Patients with refractive errors >+4 D & <–9 D, eyes with opaque hazy media e.g. advanced cataract, eyes with Diabetic retinopathy or any other cause of retinopathy, eyes with optic nerve head disease of any other etiology and eyes with retinal pigment layer disorders or rod or cone dystrophies.

All the study participants underwent full ophthalmological assessment with visual field testing using the standard automated perimetry (SAP) examinations by Humphrey Field Analyzer (Carl-Zeiss Meditec, Dublin, CA; SITA standard strategy, program 24-2. We used the visual field mean deviation (MD) for analysis and correlation with other parameters of pERG and peripapillary RNFL average thickness. All the study participants underwent OCT imaging using the OCT Spectralis (Heidelberg engineering, Heidelberg, Germany) - without use of mydriatic eye drops- with recording of nerve fiber layer thickness in the peripapillary zone. Using the 3.4 mm circular scan centered on the optic disc, the peripapillary retinal nerve fiber layer thickness was measured in the four quadrants and the average RNFL thickness was taken as the main parameter [6]. All the study participants underwent pattern ERG test using RetiMax device (CSO, Pisa, Italy) in accordance with International Society for Clinical Electrophysiology of Vision (ISCEV) guidelines. The P50 latency & amplitude, the N95 latency & amplitude and the P50-N95 latency and amplitude were recorded. The test was performed without pupillary dilatation, in dim background illumination and with the individual wearing his optical correction for near [7].

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 (IBM, Chicago, USA). For analysis of means of quantitative data between the study groups, Student *t*-test & ANOVA (Analysis of Variance) test with the least significant difference were used. Correlations between different variables were done using (Spearman correlation coefficient) non-parametric test as our data were not normally distributed. p-value of ≤ 0.05 was used as a cut off value for significance of results.

Results

The visual field mean deviation (MD) of the two main groups (normal & POAG) showed significant difference with p-value <0.001 (Table 1). Comparing the visual field MD in different subgroups of POAG also showed significant difference with p-value <0.001.

Regarding the structural changes in glaucoma, the mean RNFL thickness of the two main groups (normal & POAG) showed significant difference with p-value <0.001 (Table 2). Comparing the RNFL average thickness in different subgroups of POAG also showed significant difference with p value <0.019.

The pERG parameters of interest (P50 wave latency and its amplitude, N95 wave latency and its amplitude and P50-N95 latency and amplitude) are represented by their mean $\pm$ SD in different study groups in table 3&4. Significant difference was found in N95 latency & P50-N95 latency between normal & POAG groups (p=0.001 & 0.008 respectively).

A significant correlation was found between age and visual field MD (p=0.006), P50 latency (p<0.001) and P50-N95 amplitude (p<0.007) when analysis was performed for all the studied eyes. In our study, we found that there was a significant correlation between visual field MD and peripapillary RNFL average thickness (p<0.001) (Fig. 1). and P50-N95 amplitude (p=0.006). We found also a significant correlation between the peripapillary RNFL average thickness, N95 amplitude, P50-N95 amplitude, N95 latency and P50-N95 latency (p< 0.001, =0.002, 0.034 & 0.045 respectively) (Figs. 2,3).

In subgroup analysis, we found significant correlation between the peripapillary RNFL average thickness and N95 amplitude for the moderate POAG & severe POAG subgroups (p-value=0.005 & 0.001 respectively). (Figs. 4-6) represent visual field test, OCT measurement of RNFL, and pERG parameters of eyes with mild, moderate, and severe glaucoma, respectively.

Table (1): The visual field MD of the study group (n=65).

	Mean	S.D	(t)	p-value
The whole study eyes (65)	–8.17	7.32		
Normal (15)	–1.33	1.42		
POAG patients (50)	–10.22	7.13	4.77	<0.001 * *
POAG subgroups:			ANOVA test with LSD (p-value)	
Mild POAG (9)	–2.70	1.52		
Moderate POAG (13)	–6.35	2.37	21.39	<0.001 **
Severe POAG (28)	–14.44	6.68		

Table (2): The OCT peripapillary RNFL average thickness of the study group. (n=65)

	Mean	S.D	(t)	p-value
The whole study eyes (65)	80.86∝	23.43∝		
Normal (15)	101.20∝	8.35∝		
POAG patients (50)	74.76∝	23.07∝	4.33	<0.001 * *
POAG subgroups:			ANOVA test with LSD (p-value)	
Mild POAG (9)	85.88∝	13.90∝		
Moderate POAG (13)	84.15∝	16.91∝	4.28	<0.019**
Severe POAG (28)	66.82∝	25.16∝		

Table (3): Pattern ERG parameters in different study groups (n=65).

pERG parameter	Normal (15)		POAG (50)	
	Mean	S.D	Mean	S.D
P50 latency	49.02ms	2.77ms	51.35ms	8.57ms
P50 amplitude	2.70∝V	1.20∝V	2.58∝V	2.27∝V
N95 latency	93.42ms	9.52ms	105.29ms	17.60ms
N95 amplitude	–1.77∝V	1.16∝V	–1.28∝V	1.60∝V
P50-N95 latency	44.40ms	10.06ms	53.93ms	15.65ms
P50-N95 amplitude	4.47∝V	1.70∝V	3.87∝V	2.67∝V

Table (4): Pattern ERG parameters in different POAG subgroups (n=50).

pERG parameter	Mild POAG (9)		Moderate POAG (13)		Severe POAG (28)	
	Mean	S.D	Mean	S.D	Mean	S.D
P50 latency	48.66 ms	4.12 ms	53.93 ms	11.81 ms	51.01 ms	7.79 ms
P50 amplitude	3.42 ∝V	1.90 ∝V	2.87 ∝V	2.92 ∝V	2.92 ∝V	2.01 ∝V
N95 latency	101.94 ms	12.00 ms	108.55 ms	21.15 ms	104.85 ms	17.65 ms
N95 amplitude	–1.80 ∝V	1.35 ∝V	–0.93 ∝V	1.51 ∝V	–1.28 ∝V	1.71 ∝V
P50-N95 latency	53.27 ms	11.13 ms	54.61 ms	16.91 ms	53.83 ms	16.75 ms
P50-N95 amplitude	5.22 ∝V	3.01 ∝V	3.81 ∝V	2.41 ∝V	3.46 ∝V	2.63 ∝V

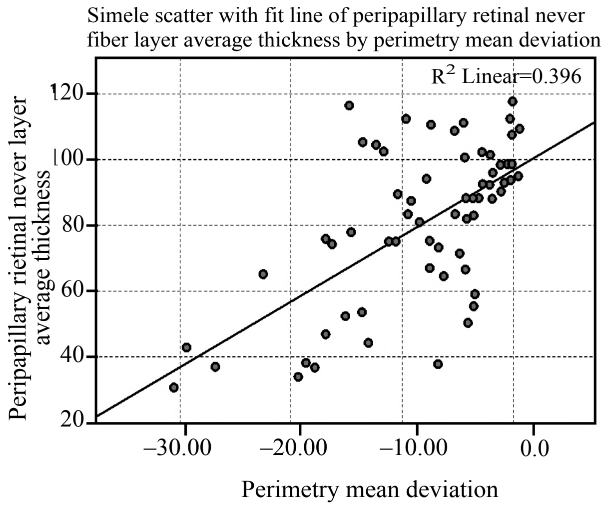

Fig. (1): Scatter plot of VF MD & peripapillary RNFL thickness in the studied eyes (n=65).

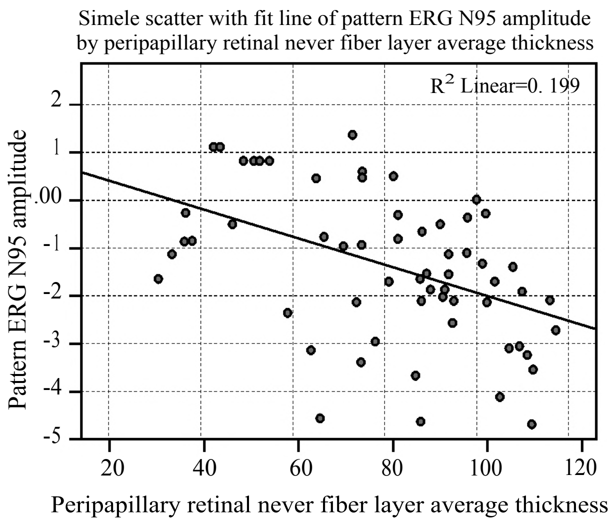

Fig. (2): Scatter plot of peripapillary RNFL thickness & pERG N95 amplitude in the studied eyes (n=65).

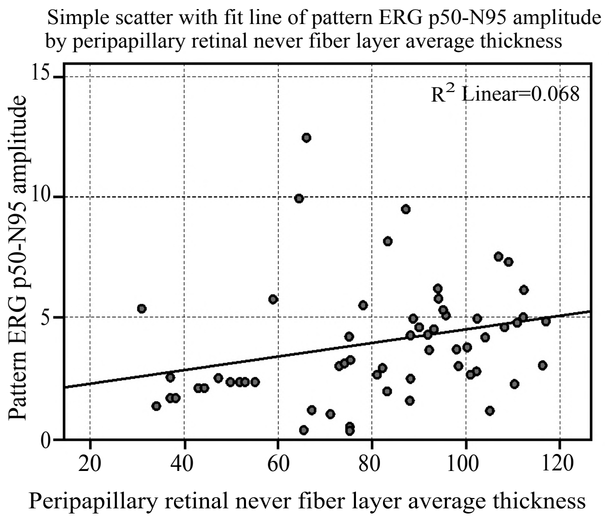

Fig. (3): Scatter plot of peripapillary RNFL thickness & pERG P50-N95 amplitude in the studied eyes (n=65).

Fig. (4):

55-year old female, BSCVA 0.8 on the decimal scale. C/D ratio was 0.5. IOP 16mmHg controlled on one topical antiglaucoma medication for 5 years, her visual field (VFMD=–3.82), peripapillary RNFL average thickness =92 t and pattern ERG are shown here.

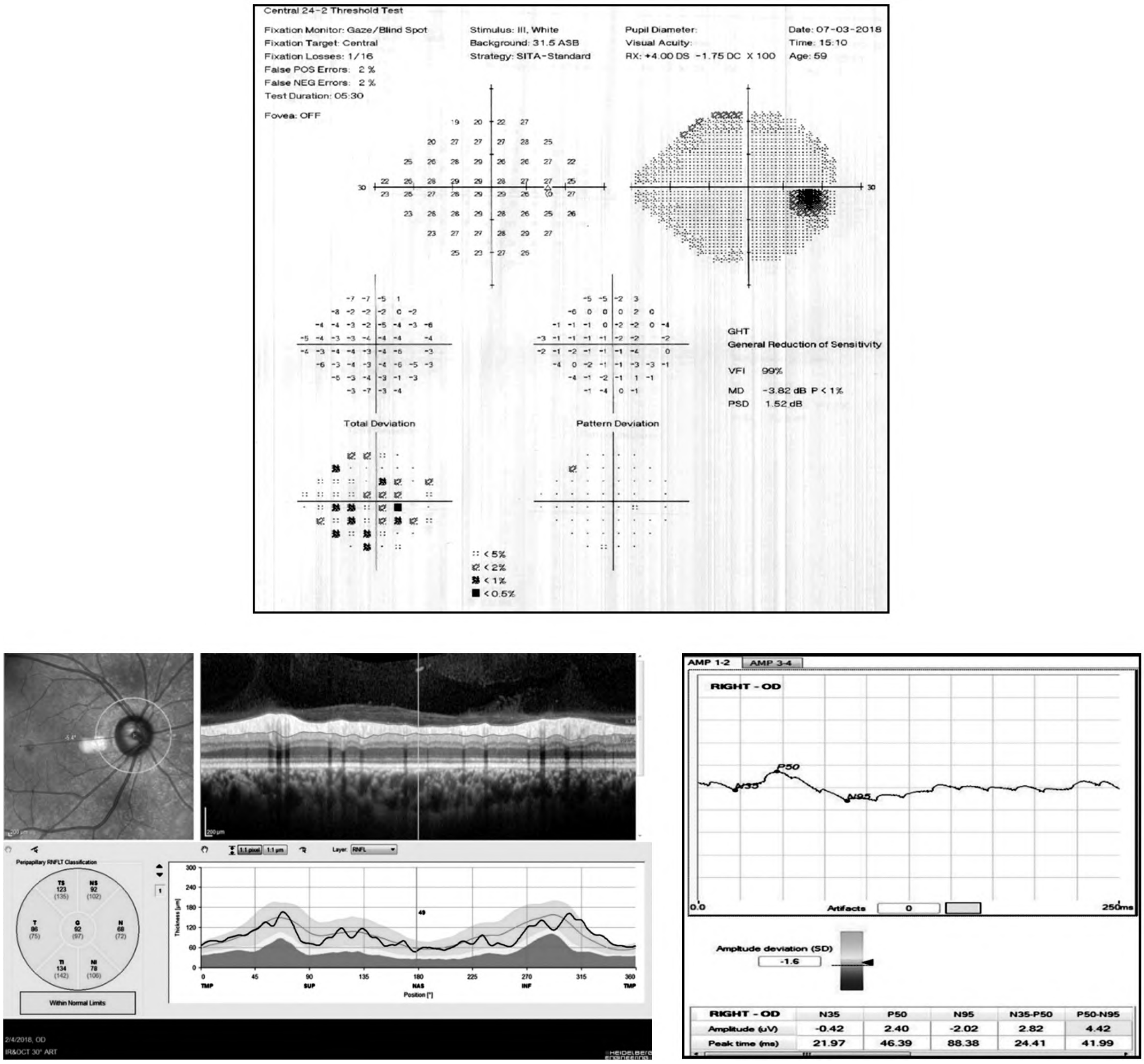

Fig. (4): VF, peripapillary RNFL thickness& PERG in mild glaucoma case. (MD = –3.82 dB, Average peripapillary RNFL thickness = 92µ & Pattern ERG shows low amplitude of its waves.

Fig. (5):

74-year old male, BSCVA 0.5 on the decimal scale, C/D ratio was 0.6, IOP 16mmHg controlled on three topical antiglaucoma medications for 9 years, his visual field (VFMD=–7.62), peripapillary RNFL average thickness =82 g and his pattern ERG are shown here.

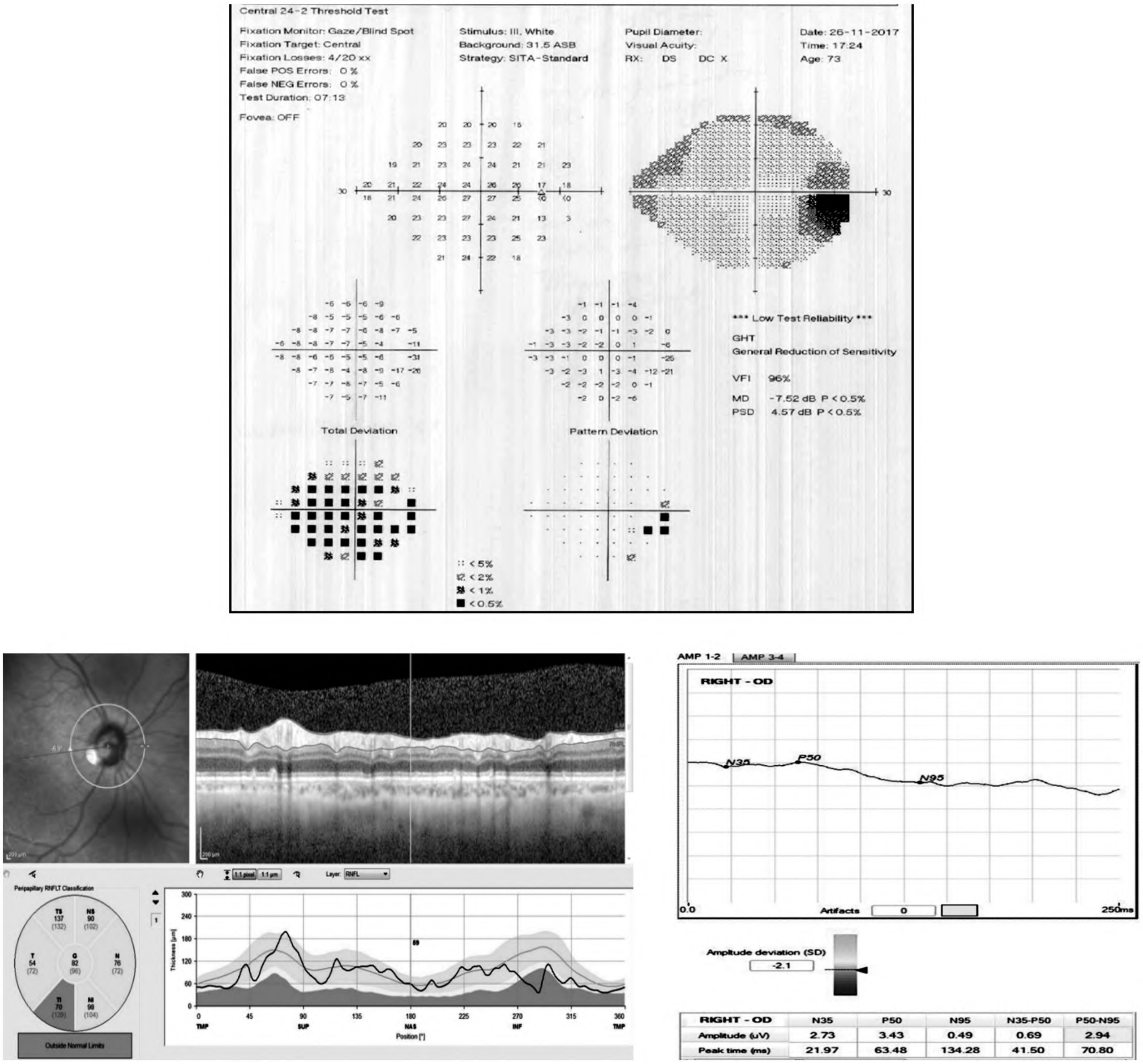

Fig. (5): VF, peripapillary RNFL thickness& PERG in moderate glaucoma case. (MD = –7.62 dB, Average peripapillary RNFL thickness = 82U & Pattern ERG shows very low amplitude of its waves.

Fig. (6):

52-year old male diabetic and hypertensive for 10 years. BSCVA 0.9 on the decimal scale. C/D ratio was 0.8, IOP 18 mmHg. Controlled on two topical antiglaucoma medications for 3 years, his visual field (VFMD =–13.61), peripapillary RNFL average thickness =73 t and his pattern ERG are shown here.

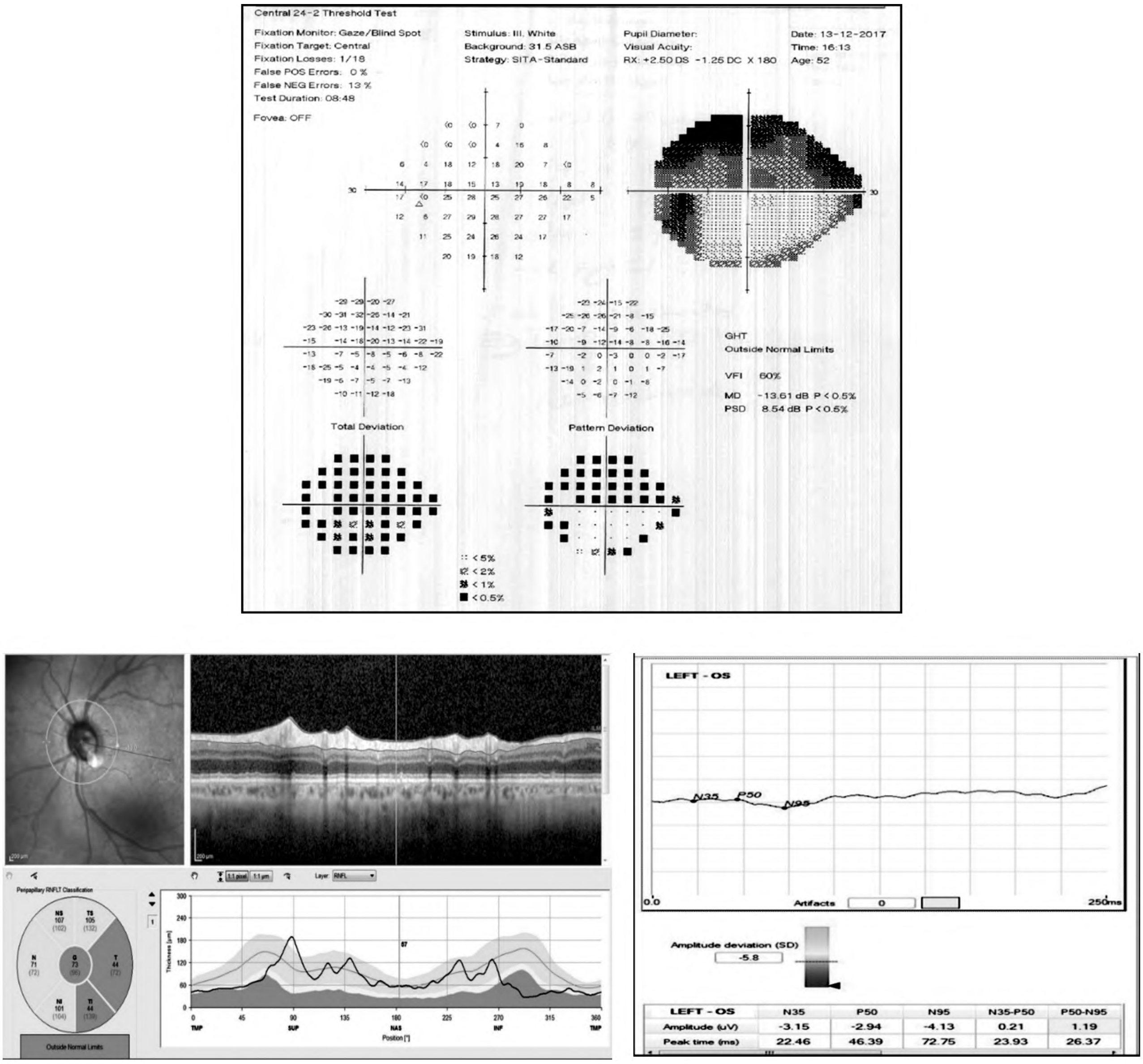

Fig. (6): VF, peripapillary RNFL thickness& PERG in severe glaucoma case. (MD=–13.61dB, Average peripapillary RNFL thickness = 73μ & Pattern ERG appears nearly flat pERG.

Discussion

Visual field mean deviation is the main parameter used in our study with an average of –8.17 for the whole study group (–1.33 for the normal group & –10.22 for the POAG group). In severe glaucoma subgroup we had an average MD of –14.44. These figures can be attributed to the relatively large number of severe glaucoma patients in the POAG group. In comparison to what North, et al., found in their study in 2010 which included 30 OAG patients, 23 subjects with OHT and 28 healthy individuals in a normal control group. The mean deviation was as follows for their study groups (–1.89, –0.85 & 0.14) respectively [12]. Park, S et al., (2017) results coincide with our results as they had the following average visual field MD (–0.97, –3.23 & –12.2) for their three groups; normal, early glaucoma and advanced glaucoma respectively [13].

Bussel, et al., (2014) based on their review of the evidence to that date, concluded that retinal nerve fiber layer remains the dominant parameter for glaucoma diagnosis and detection of progression **[14]**. In their study, Moreno and associates, measured both the ganglion cell complex and peripapillary RNFL thickness which showed nearly similar capability for differentiation between healthy and early glaucomatous eyes **[15]**. Demir, et al., (2015) reported significant correlation between RNFL and GCC parameters in the POAG group and in the OHT group. Depending on their results, using RNFL thickness in our study as the main parameter for measuring the structural defects in glaucoma is not inferior to the use of retinal GCC **[16]**.

The average peripapillary RNFL thickness in the eyes of this study was 80.86 (101.2 for normal group & 74.76 for the POAG group). North, et al., in their study in 2010 had mean global RNFL thickness of (112.42 for normal group, 116.25 for OHT group & 104.66 for open-angle glaucoma group) **[12]**. This difference from our POAG group average RNFL thickness may be attributed to the relatively higher proportion of advanced glaucoma cases in our study group which had thinner average peripapillary RNFL thickness.

Regarding pERG parameters we used in our study, both N95 latency & P50-N95 latency were significantly different between the normal and POAG groups. These results differ from what Cvenkel, et al., concluded in their study in 2017 for assessment of the ganglion cell loss in early glaucoma. They did not include P50 nor N95 latency in their study. They found that both P50 and N95 amplitudes are sensitive for detection of early glaucoma, while only N95 amplitude could differentiate glaucoma suspect from healthy eyes **[17]**.

Peripapillary RNFL average thickness of our study group showed strong correlation with pERG N95 amplitude & P50-N95 amplitude. Cvenkel, et al. had different results in their study in 2017. They found that pERG P50 amplitude showed stronger correlations only for peripapillary retinal NFL thickness **[17]**. This relationship may be more obvious for early glaucoma stages in their study and it could have been masked by the relatively large proportion of advanced glaucoma cases in our study.

Demir, et al., (2015) also agrees with our study regarding the significant difference of pERG amplitudes in POAG and normal group, they found that pERG amplitudes were lower in the POAG and OHT groups than in the control group with greater reduction in N95 amplitude than that of P50. They also concluded that dysfunction of ganglion cells in patients with OHT may be detected earlier than OCT or visual field defects using pERG amplitude analysis **[16]**. Park and his associates, (2017) in their study for correlation between macular structure and function using spectral domain-optical coherence tomography (SD-OCT) and pattern electroretinograms; they concluded that pERG amplitude was significantly correlated with macular GCIPLT in early glaucoma patients, but visual field test results showed no correlation with macular ganglion cell-inner plexiform layer thickness (GCIPLT) and pERG **[13]**.

The importance of retinal electrophysiology tests particularly pERG is that they could detect functional damage of the retinal ganglion cells in its early and theoretically reversible stage. This advantage of pERG was proved by Guadilla, et al. in 2016 as they performed a prospective study with 126 patients (197 eyes) classified into 3 groups: Patients with OH who were treated with ocular hypotensive drops, patients with OH who were not treated and a control group. They studied the changes in pERG values between initial exploration and a follow-up after 6 months. They reported a statistically significant improvement in pERG P50 and N95 amplitudes in the OHT group who received topical antiglaucoma medications in comparison to the non-treated group. They found no statistically significant difference in wave latencies **[18]**.

Conclusion:

Pattern ERG parameters including the N95, the P50-N95 amplitudes & the N95, P50-N95 latencies showed significant correlation with the peripapillary RNFL average thickness. Pattern electroretinogram, as a measure for ganglion cell dysfunction, in combination with optical coherence tomography for structural assessment of the optic nerve head and peripapillary retinal nerve fiber layer-can be very helpful in glaucoma diagnosis especially when reliable perimetry cannot be obtained.

Recommendations: A larger sample-size study need to be conducted and followed on a longitudinal basis to check the sensitivity of pattern electroretinogram to detect progression of ganglion cell dysfunction. We also recommend studies on closer age to develop a normative database for pERG in glaucoma patients. Studies that combine pattern electroretinogram as a global assessment of retinal ganglion cell function & multifocal electroretinogram which signifies localized defects in visual field and peripapillary retinal nerve fiber layer are to be undertaken.

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دراسة الارتباط بين التغيرات التكوينية والوظيفية فى مرضى المياه الزرقاء بإستخدام التصوير المقطعى المترابط ورسام الشبكية الكهربائى النمطى

تعد المياه الزرقاء أحد أهم الأسباب الأساسية للعمى الذى لا رجعة فيه فى العالم. وتمثل مجموعة منالأمراض التى يتم تعريفها بإعتلال العصب البصري المميز لها مع وجود تغيرات مميزة للمرض فى مجال الأبصار. وقد تم قبول قياس سمك طبقة الألياف العصبية بالشبكية بإستخدام التصوير المقطعى المترابط كأداة مهمة لتشخيص الخلل التكوينى فى مرض المياه الزرقاء. فهو أختبار موضوعى، سهل القيام به وسهل قراءته.

ويعد مجال الأبصار هو الأداة الأساسية لأكتشاف أى فقدان فى مجال الأبصار. ومع ذلك فإن هذا الأختبار له عيوبه: فهو يحتاج لتعاون المريض ويستغرق وقتاً طويلاً كما أنه يكتشف التغيرات المميزة للمياه الزرقاء بعد فقدان ٣٠ إلى ٤٠٪ من الألياف العصبية للشبكية. ولذلك فهو ليس الأداة المناسبة لأكتشاف المرض فى مراحله الأولى.

وقد أجريت أبحاث كثيرة فى مجال رسام الشبكية الكهربائى النمطى بإعتباره أختبار موضوعى لتقييم وظيفة الشبكية. مما يتيح الفرصة لهذا الأختبار للمساعدة فى تشخيص مرض المياه الزرقاء جنباً إلى جنب مع التصوير المقطعى المترابط للعصب البصرى.

هذا البحث هو دراسة مقطعية تشمل ٥٠ عيناً لمرضى المياه الزرقاء الأولية مفتوحة الزاوية فى مختلف مراحل المرض (البسيطة والمتوسطة والمتقدمة) و١٥ عيناً ل ١٥ شخص طبيعى يمثلون المجموعة الضابطة.

وتهدف إلى دراسة العلاقة بين قياسات التصوير المقطعى المترابط لطبقة الألياف العصبية بالشبكية كدلالة على التغيرات التكوينية والتغيرات فى رسام الشبكية الكهربائى النمطى كدلالة على التغيرات الوظيفية فى مرضى المياه الزرقاء مفتوحة الزاوية.

وقد تم تقييم كل المشاركين فى الدراسة تقييماً كاملاً من ناحية دب العيون يشمل ما يلى:

- أختبار مجال الأبصار بإستخدام نظام قياس مجال الأبصار همفرى مع الأستراتيچية ٢-٢٤.
- التصوير المقطعى المترابط لطبقة الألياف العصبية بالشبكية بإستخدام جهاز هيلدلبيرج مع تسجيل سمك طبقة الألياف العصبية بالشبكية فى الأربعة أرباع لمنطقة ما حول القرص البصرى ثم أخذ متوسط السمك.
- أختبار رسام الشبكية الكهربائى النمطى وفقاً للمبادئ التوجيهية للجمعية الدولية لدراسة كهربية الرؤية مع تسجيل أرتفاع ومدى تأخر كل من الموجات الآتية: P50 & N95 وكذلك الفرق بين الموجة الموجبة و الموجة السالبة من خيث الأرتفاع ومدى التأخر.

خلصت دراستنا لوجود علاقة بين متوسط سمك طبقة الألياف العصبية بالشبكية حول القرص البصرى وبين بعض العوامل التى تم قياسها فى أختبار رسام الشبكية الكهربائى النمطى مثل أرتفاع الموجة N95 وكذلك الفرق فى أرتفاع الموجتين الأساسيتين P50 وN95. كما أظهرت أيضاً وجود علاقة بين متوسط الأنحراف فى مجال الأبصار والفرق بين أرتفاع الموجتين الأساسيتين.

وأيضاً أثبتت دراستنا العلاقة بين متوسط سمك طبقة الألياف العصبية بالشبكية حول القرص البصرى ومتوسط الأنحراف فى مجال الأبصار مما يثبت العلاقة بين التكوين والوظيفة.

وعند تقسيم مجموعة البحث إلى مجموعتين رئيستين، توصلنا لوجود علاقة وثيقة بين متوسط الأنحراف فى مجال الأبصار ومتوسط سمك طبقة الألياف العصبية بالشبكية حول القرص البصرى فى المجموعة المصابة بمرض المياه الزرقاء.

وقد توصلنا لوجود علا قة وثيقة بين متوسط سمك طبقة الألياف العصبية بالشبكية حول القرص البصرى وبين بعض العوا مل التى تم قياسها فى أختبار رسام الشبكية الكهربائى النمطى مثل أرتفاع الموجة N95 و كذلك الفرق فى أرتفاع الموجتين الأساسيتين P50 وN95 فى المجموعة المصابة بمرض المياه الزرقاء.

الخلاصة: خلصت دراستنا للتالى:

- يمكن إستخدام رسام الشبكية الكهربائى النمطى للتقييم الموضعى لوظيفة خلايا العقدة بالشبكية مما يمهد الطريق لإستخدامه لتشخيص وربما متابعة مرضى المياه الزرقاء.
- يمكن أن يحل رسام الشبكية الكهربائى النمطى محل مجال الأبصار فى المرضى غير المتعاونين أو الذين لا يفهمون أختبار مجال الأبصار.

الجمع بين رسام الشبكية الكهربائى النمطى وقياس سمك طبقة الألياف العصبية المحيطة بالعصبالبصرى يساعد كثيراً فى تشخيص مرضى المياه الزرقاء خاصة عند الفشل فى الحصول على نتائج يعتمد عليها من أختبار مجال الأبصار.