Neuroretinal evaluation using optical coherence tomography in patients affected by pituitary tumors

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Yasar Altun*, Ayse Sevgi Karadag**, Seyho Cem Yucetas***, Sadullah Saglam*, Ali Zeynal Abidin Tak*, Ilhan Cag*, Yusuf Ehi*

**Adiyaman University Training and Research Hospital, Department of Neurology, Adiyaman, Turkey*
***Adiyaman University Training and Research Hospital, Department of Ophthalmology, Adiyaman, Turkey*
****Adiyaman University Training and Research Hospital, Department of Neurosurgery, Adiyaman, Turkey*

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AIM: *To investigate the thickness of the retinal nerve fiber layer (RNFL), the ganglion cell layer (GCL), inner plexiform layer (IPL), and choroid thickness (CT) in patients with pituitary tumours, microadenoma and macroadenoma, using spectral optical coherence tomography (OCT).*
METHODS: *Thirty six patients who had micro and macroadenoma, and 34 healthy participants (control group) were included in the study. Spectral OCT was used to measure the RNFL, GCL, IPL, and CT values for all patients. CT measurements were performed by the same author (A.S.K). Additionally, retinal nerve fiber length, which is a sublayer of ganglion cell complex (GCC), was also measured for each patient and after segmentation oF GCC.*
RESULTS: *No difference was detected between group according to sociodemographic data. The mean age of patients and the control group was 34.31 ± 12.47 and 33.12 ± 11.75 years, respectively. In the patient group had RNFL thinning while there was a thickening of the choroid layer. When all pituitary tumours patients (without grouping) were compared with the control group and there were significant differences on all parameters: RNFL, GCL, IPL thickness, and CT ($p<0.05$), while there were no significant differences in RNFL and GCL measurements between microadenoma and macroadenoma ($p>0.05$). All patients were significantly different from one another with respect to CT ($p<0.05$).*
CONCLUSIONS: *These findings suggest that neurodegeneration occurs in the course of pituitary tumours, and this degeneration may be presented by decreased GCL at early stages, and as the disease progresses it may also affect ather layers of GCC like RNFL and IPL. RNFL and GCL were significantly thinner in the all patients as compared with the control subjects. In pituitary tumours, both microadenoma and macroadenoma, when evaluating ophthalmological findings patients' choroid thinning should be considered.*

KEY WORDS: Choroid thickness Ganglion cell layer thickness, Optical coherence tomographyl Pituitary tumours, Retinal nerve fiber layer thickness

Introduction

Pituitary adenomas are the most common tumours of the sellar region. They generally have a slow but severe impact on vision due to compression of the optic nerves, optic chiasm and cavernous sinus. Pituitary tumours account for approximately 15 to 17% of all intracranial neoplasms [1-3]. The majority is benign, non-invasive and asymptomatic. Some are detected incidentally by imaging exams; others are functioning-tumours generating hormonal syndromes (in decreasing ordered: prolactin, adrenocorticotropic hormone growth hormone, thyroid-stimulating hormone, follicle-stimulating hormone, and luteinizing hormone), whereas others are suspected due to local mass symptoms. Hypopituitarism can also occur in some cases, particularly in larger tumours[4]. Pituitary adenomas display an array of hormonal and proliferative activity. Once primarily

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Correspondence to: Dr Yasar Altun, Adiyaman University Training and Research Hospital, Department of Neurology, Adiyaman, Turkey (e-mail-mail: yasaraltun02@gmail.com)

classified according to size (microadenomas, ≤ 1 cm; macroadenomas, ≥1 cm)[3]. Studies investigating tumor size and morphologic appearance have also shown conflicting results [5-7].

Optical coherence tomography (OCT) is a rapid, and noninvasive method that can assess macula thickness (MT) and volume (MV) of retinal layers [8]. Especially with today's OCT technology resolution is enhanced and segmentating retinal layers such as ganglion cell layer (GCL), inner plexiform layer (IPL), and retinal nerve fiber layer (RNFL) is now possible [9]. RNFL involves axons of ganglion cells, GCL involves bodies of ganglion cells, and IPL involves dendrites of ganglion cells [10]. Another parameter that can be measured with OCT is choroidal thickness (CT). Choroid is among the most vascularized tissues in human body and it has important roles in oxygenization and nutrition of outer retina, temperature regulation of the retina, arrangement of the position of retina, disposition of waste products from retina, and release of growth factors [11]. So, any vascular pathology can cause choroidal thinning [12]. So far, most studies on structure-function relationships have used RNFL thickness measurements to evaluate axonal damage. However, several studies have indicated that macular thickness measurements may also be used as an indicator of neural loss. Because the GCL accounts for up to 40% of the thickness in the macular area, estimates of macular thickness can be used to investigate possible ganglion cell loss. The measurement of RNFL by OCT has been proposed as a way to verify axonal loss [13]. Owing to technological advances in recent years, the new-generation spectral domain OCT instruments that use improved scanning speed and special software techniques (EDI) enable the acquisition of high-resolution images OCT [14], which can perform reproducible, non-invasive in vivo evaluations, has come into clinical use as an imaging method for evaluating the thickness of the optic nerve head, peripapillary RNFL, GCL, and choroid layers in various neuro-ophthalmologic diseases [15,16]. Ganglion cell complex (GCC) analysis can provide more sensitive measurements [17]. Because of retrograde degeneration of the ganglion cell axons and thinning of the nasal and temporal RNFL [18,19], future advances in OCT technology will allow further improvements in the detection and quantification of optic nerve dysfunction and subtle changes in nerve head morphology resulting from ocular tumours.

Although some studies have investigated the RNFL thickness in patients who have pituitary tumours by using OCT and scanning laser polarimetry [18,20,21], so farm no study has been conducted to investigate on the GCL, IPL, and CT in microadenoma and macroadenoma patients. Therefore, the purpose of the present study was to investigate potential differences in RNFL, GCL, IPL, and CT between patients who have microadenoma and macroadenoma.

Methods

Study Design

This is a prospective case-control study which compared pituitary tumours patients group and a control group. This study included 36 pituitary tumours patients (29 women, 7 men, aged 34.31±12.47 years, 72 eyes). Patient group divided into two groups (microadenoma and macroadenoma) who were being followed in Neurology and Neurosurgy Department of Adiyaman University Medical School and 34 healthy volunteers (25 women, 9 men, aged 33.12±11.75 years, 68 eyes) without pituitary adenoma and with a normal ophthalmic examination served as the control group. Healthy subjects at least 18 years of age were invited to participate in this study. In addition, subjects with retinal diseases, obvious glaucomatous optic neuropathy, and severe cataract or vitreus opacity were excluded from the study. Healthy control eyes also had healthy-looking optic discs and RNLF. Visual field and visual evoked potential could not be used in our study. This study was approved by local ethical committee (Adiyaman University, Human Ethics Committee, Meeting: 2015/03-8, Adiyaman, Turkey). Both groups were informed about the study procedure and signed written informed consent forms.

Sociodemographic data forms (including age, sex etc) were filled for each patient and control OCT assessments were performed by Ophthalmology Department of Adiyaman University Medical School. Spectral OCT was used to measure the RNFL, GCL, IPL, and CT values for all patients.

Patient Selection

All participants underwent a complete neuro-ophthalmic evaluation that included pupillary, anterior segment, and funduscopic examinations; assessment of logMAR best corrected visual acuity (BCVA). Both eyes of each subject were included. The main inclusion criteria were: age > 18 years; evidence at pituitary magnetic resonance imaging (MRI) of a pituitary micro and macroadenoma without chiasm impingement; written informed consent to study participation. Exclusion criteria were: any previous treatment for pituitary adenoma; presence of congenital eye disorders; myopia > 6 dioptres; a history of ocular surgery; significant lens opacities or any macular disease; a previous diagnosis of glaucoma; and any optic disc anomaly.

OCT Measurement

Right and left eyes RNFL, GCL, IPL, and CT measurements were performed with Spectralis (Heidelberg Engineering GmbH, Heidelberg, Germany) OCT device. Choroid thickness measurements were performed by the same author (A.S.K). RNFL is divided into temporal (T)

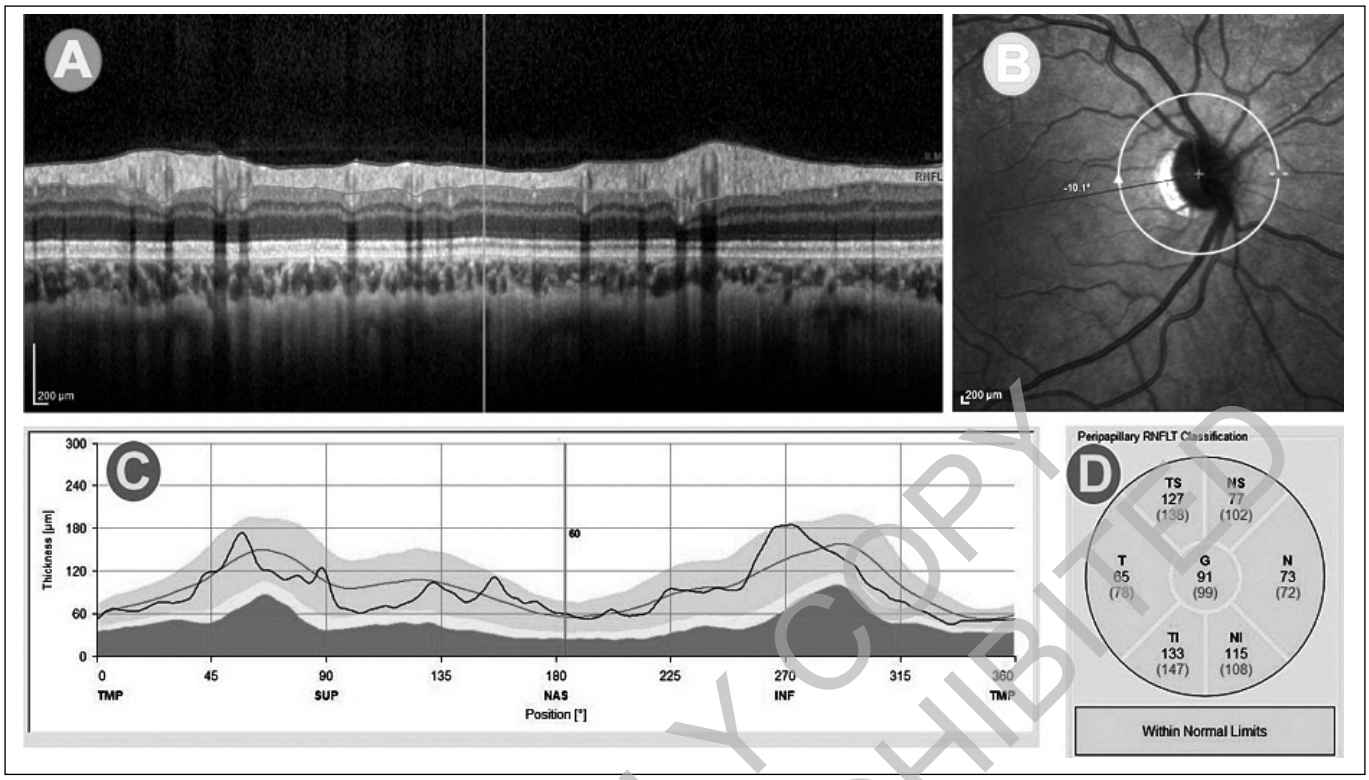

Fig. 1: Measurement retinal nerve fibre layer (RNFL) thicknesses with spectral optic coherence tomography (OCT) of normal classified eye. **A**) A circle is drawn around the optic disc to measure peripapillary RNFL thickness. **B**) A picture demonstrating the RNFL. **C**) Seven measurements are performed for each eye, providing the RNFL thicknesses of the temporosuperior (TS), temporo-inferior (TI), temporal (T), nasal superior (NS), nasal inferior (NI), nasal (N) and global (G) sectors. **D**) RNFL thickness map.

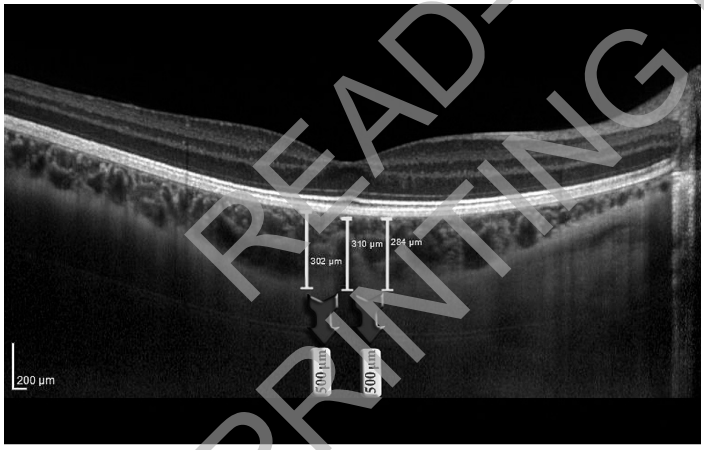

Fig. 2: Measurement of the choroidal thickness by spectral optic coherence tomography (OCT). A perpendicular line (middle yellow line) is drawn subfoveal from the outer edge of retinal pigment epithelium-choriocapillaris complex to the choroid-sclera junction. Two additional lines are drawn at the nasal and temporal sides at 500 mm intervals from the subfoveal line. The mean value of these 3 measures was accepted as the choroidal thickness that include 2 principal layers of sattler(little vessels) and df haller (large vessels).

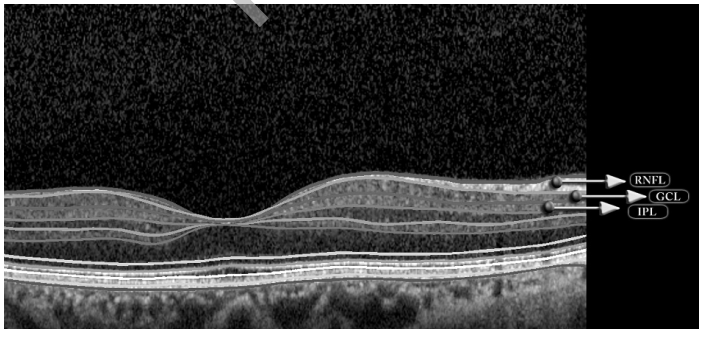

Fig. 3: Measurement of the retinal nevre fibre layer (RNFL), ganglion cell layer (GCL) and inner plexiform layer (IPL) thicknesses with spectral optic coherence tomography (OCT).

and nasal (N) halves and these are divided into superior (S) and inferior (I) quadrants automatically by spectral OCT device. In conclusion we compared 6 regions (N, NS, NI, T, TS, TI) and mean RNFL from right and left eyes with controls (Fig. 1). This measurement was made by using measurement tool of the OCT device. Manually, a vertical line was drawn from outer layer of retinal pigment epithelium to choroid-sclera border and its length was recorded. Three different measurements were performed from fovea to nasal and temporal poles with 500 m intervals (Fig. 2). We calculated mean CT from separate measurements of three regions and compared the two groups accordingly. Lastly, we segmentated GCC into RNFL (the axonal component), GCL (cell body component), and IPL (dendritic component) and made comparisons for each layer (Fig. 3).

Statistical Methods

Statistical analyses were performed using SPSS 21.0 package program (IBM Corp, Armonk, NY). The mean ± standard deviation and percentages were used as descriptive statistics. The normality of the data was tested using the Kolmogorov-Smirnov test. The Chi-square test was used to compare categorical variables. Independent samples t-test was used to compare 2 normally distributed variables and the Mann-Whitney U test was used to compare 2 non-normally distributed variables. The generalized estimating equations (GEE) method was used to compare the RNFL thicknesses and GCL and IPL volumes between the patient and control groups. GEE is an established method of analyzing paired biological data (e.g., OCT data from a pair of eyes), which enables using data from both eyes and protects from a conflation of statistical significance that can result from the use of paired biological data from the same subject (i.e., pair of eyes) [22] $p<0.05$ indicated statistical significance.

Results

Sociodemographic Data

The study group included 36 patients and 34 controls. Mean age of the patient group was 34.31±12.47 and the control group was 33.12±11.75. The patient group consisted of 29 females (80.6%) and 7 males (19.4%). The control group consisted of 25 females (73.5%) and 9 males (26.5%). Sociodemographic features of the patient and the control groups are given in Table I.

Table I - *Sociodemographic features.*

	Patient n = 36	Control	P value
Participants, n	36	34	
Eyes, n	72	68	
Age, years	34.31 ± 12.47	33.12 ± 11.75	0.683*
Male	7	9	0,484**
Female	29	25	

*Independent samples t-test; **chi square test

OCT Data

RNFL Findings

Decreases were observed in some parts of RNFL in the patient group. Among RNFL parts decreases in N, TS, T, TI and mean RNFL were statistically significant ($p<0.05$), while NS and NI were not statistically significant.

Mean Choroidal Thickness

Choroidal thickness was calculated by getting mean value of 3 assessments from different areas. Choroidal thickness compared to the patients and control groups showed a statistically significant increase in the patient group. Choroidal thickness was statistically significant in patients group between patient and the control groups ($p<0.05$) (Table II).

Ganglion Cell Layer Findings

Thicknesses of GCL were significantly decreased in the patient group ($p<0.05$) (Table III).

Discussion

Recent studies based on segmented OCT macular thickness measurements have demonstrated that the presence of retinal ganglion cell (RGC) loss may be an early indicator of neural loss in conditions, such as glaucoma, multiple sclerosis, and neuromyelitis optica [23-27].
Demonstration of retinal myelin loss with OCT forms a great evidence for degeneration [28]. Therefore, retina layer thickness has become an important anatomical structure to follow neurodegeneration. Previous studies have evaluated RNFL and GCC thickness in patients with pituitary adenomas, especially in those with chiasmal compression [18,27,29]. The presence of pituitary tumour, even in the absence of compressive effect at the chiasm on MRI, may cause reversible RGC dysfunction, which precedes visual field loss and RGC death as supported by the unaffected RNFL-OCT [30]. In addition, in a new study conducted on pituitary macroadenoma with no optic chiasmal compression, they have found RNFL and GCC in the patient group thinner than controls. They have attributed this result to the fact that may cause thinning

TABLE II - *Comparisons of RNFL and macula thicknesses in microadenoma and macroadenoma patients and controls.*

Parameter	Patient/Control	Mean±SD (µm)	*p value (All adenoma patients vs. controls)	*p value (Microadenoma vs. macroadenoma)
Global	Microadenoma	99.43±11.28	0.000	0,271
	Macroadenoma	95.93±15.46		
	Control	109.47±23.56		
Nasal Superior	Microadenoma	115,30±19,85	0,079	0,071
	Macroadenoma	106,21±21,53		
	Control	118,00±20,85		
Nasal Inferior	Microadenoma	119,93±26,45	0,709	**0,288**
	Macroadenoma	113,04±27,01		
	Control	118.93±26.25		
Nasal	Microadenoma	74.00±13.23	0,004	0,117
	Macroadenoma	68.25±17.41		
	Control	79.10±14.76		
Temporal Superior	Microadenoma	133.86±19.93	0,000	0,817
	Macroadenoma	135.07±23.85		
	Control	147.71±15.79		
Temporal Inferior	Microadenoma	144.91±25.43	0,002	0,929
	Macroadenoma	144.32±30.19		
	Control	157.00±16.50		
Temporal	Microadenoma	70.50±13.58	**0,001**	**0,388**
	Macroadenoma	67.75±12.29		
	Control	75.87±8.83		
Choroid Mean Value	Microadenoma	319.77±55.55	0,000	0,275
	Macroadenoma	302.93±73.90		
	Control	258.15±37.10		

*Generalized estimating equations (GEE)

TABLE III - *Comparisons of GCL and IPL volumes in microadenoma and macroadenoma patients and controls.*

Parameter	Patient/Control	Mean±SD (µm)	*p value (All adenoma patients vs. controls)	*p value (Microadenoma vs. macroadenoma)
GCL	Microadenoma	1.12±0.11	0,000	0,497
	Macroadenoma	1.10±0.15		
	Control	1.21±0.06		
IPL	Microadenoma	0.93±0.07	0,004	0,600
	Macroadenoma	0.92±0.11		
	Control	0.96±0.06		

*Generalized estimating equations (GEE)
GCL: Ganglion cell layer, IPL: Inner plexiform layer

in the RNFL and GCC, though pituitary tumours do not make chiasmal compression [31]. In our study, whether or not they were viewed in optical chiasmal compression in patients than controls were found thinner RNFL and GCC. In addition, IPL values have been detected to be much thinner than in the patient group. In this study, our results similar to Cennamo et al. results [31]. In our study, it may be possible that micro-compression was missed by the MRI. On the other hand, the GCC loss might be related to interference in axoplasmic flow induced by local ischaemia at the level of optic chiasm[32]. This hemodynamic change might be related to the act of vasoactive peptide endothelin-1 that is released by pituitary tumours [33]. OCT is a useful tool because it provides an objective and very reproducible measurement of RNFL thickness. OCT is also a quick test that requires

little cooperation from the patient, making it particularly useful in patients who cannot perform visual field (VF) testing reliably [34]. Subfoveal CT varies greatly according to race and sex. This study is the first to show that, in addition to macular GCC, macular RNFL and GCL might be good candidates for diagnosing pituitary tumour. This specific pattern of OCT macular damage might be helpful in differentiating pituitary tumour with a different pattern of ganglion cell loss. Our study is establish a clinical marker that correlates strongly with the degree of visual recovery in patients with pituitary tumours. The degree of reversibility of visual dysfunction with compression of the anterior visual pathway is related to the loss of RNFL thickness, as measured by the OCT. Moreover we show that the presence of pituitary tumours may impair RGC electrical activity. In addition, in our study there has been no significant relationship between IPL and microadenoma and macroadenoma.

Morgan's study data was a very modest increase in RNFL thickness in eyes overall, which was of greater magnitude in those with thin RNFL than in normal RNFL eyes. In our study, in the patients with pituitary adenoma, similar to Morgan's study, RNFL thickness has been found to be much thinner than in normal subjects. In addition, GCL and IPL values have been detected to be much thinner than in the patient group. It may be that RGC whose axons are injured at the chiasmal area undergo an initial phase of reversible injury before axon and cell body loss that involves individual axon thinning [35].

Johansson documented that the pattern of RNFL loss did not correlate well with the visual field defect. Sensitivity of RNFL thickness measurement in OCT was low. They showed that OCT at best can be used as a complementary examination in patients with pituitary adenomas, but the method has limited value in the diagnosis of pituitary tumour compression [18]. Our results did not not support the Johansson's study. Because we identified the differences by examining the IPL and GCL parameters with high sensitivity.

Monteiro documented that macular RNFL and combined retinal GCL and IPL (GCL-IPL) thicknesses estimated in different quadrants of the macula were reduced significantly in patients compared to controls. The RNFL and GCL-IPL measurements were reduced significantly in the nasal retinal quadrants as well as in the temporal retinal quadrants [27]. Monteiro also showed that MT and RNFL thickness were both significantly smaller in eyes with band atrophy of the optic nerve than in healthy control eyes, which is in agreement with several previous studies [36]. Interestingly, the inferior RNFL thickness has also been found to be a strong prognostic factor in Danesh-Meyer and associates study [19], even though findings in the other quadrants were not described. In our study, the values of RNFL and GCL were found to be similar to Monteiro's.

In the present study, we documented that RNFL and GCLs thicknesses estimated in different quadrants of the macula were reduced significantly in patients compared to controls. We also investigated the usefulness of segmenting retinal layers and obtaining thickness measurements in quadrants for improving performance in the assessment of structure-function relationships in patients with temporal field defects. Our findings clearly indicated improved performance for segmented retinal layers compared to total retinal thickness measurements of the retina for studies of structure function relationship.

The benefit in having such a clinical biomarker that is rapid, noninvasive, and convenient to measure is its usefulness in planning of management strategies including the timing of surgery, counseling patients on prognosis, and potentially monitoring disease progression. Further investigation is warranted to corroborate these preliminary findings in larger studies and in wider a range of underlying diseases.

Conclusion

Findings of this study suggest that there is neuronal degeneration in pituitary tumour; it can be understood by thinning of GCL, RNFL and IPL sublayers of retina. RNFL, IPL, and its sublayers may be used as a marker to show degeneration and follow progression in many neurological disorders. RNFL thinning reflects the amount of retinal ganglion cell degeneration caused by compression of the anterior visual pathways by a pituitary adenoma. Maybe our eyes are literally 'twindoors opening to brain'.

Limitation

Relatively small study group is a limitation of this study. Also to confirm progression of degeneration with increasing disease duration comparisons between patients who have long disease durations and newly diagnosed patients or following a patient cohort for years with regular measurements may be helpful. Lack of MRI to exclude pituitary tumours in control subjects was another limitation of our study

Strengths

Segmentation and measurement of retinal layers were made by the device so observer bias was eliminated. This was the first study in pituitary tumour patients that specifically assessed ganglion cell layer with OCT.

Riassunto

Scopo di questo studio è quello di valutare l'ispessimento dello strato di fibre nervose della retina (RNFL), lo strato delle cellule gangliari (GCL), lo strato plessifome interno (IPL) e l'ispessimento coroideo (CT) in pazienti affetti da microadenoma e macroadenoma ipofisario, usando la tomografia di coerenza ottica spettrale (OCT).

Nello studio sono stati considerati 36 pazienti affetti da micro- o macroadenoma ipofisario, e 34 pazienti sani per controllo. La tecnologia OCT è stata usata per misurare i valori di RNFL, GCL, IPL e CT in tutti. Le misurazioni CT sono state effettuate dallo stesso Autore (A.S.K). Inoltre è stata misurata anche in tutti i pazienti la lunghezza delle fibre nervose della retina, che è una sottolamina del complesso di callule gangliari (GCC) e dopo segmentazione del GCC.

Nel risultato non sono state riscontrate differenze tra i gruppi da riferire alle caratteristiche socio-demografiche. L'età media dei pazienti e del gruppo di controllo era rispettivamente di 34.31 ± 12.47 e di 33.12 ± 11.75 anni.

Nel gruppo di controllo si è riscontrato un assottigliamento del RNFL a fronte di un ispessimento dello strato coroideo. Nella comparazione di tutti i pazienti con tumore, senza differenze, con il gruppo di controllo si sono riscontrate differenze in tutti i parametri: ispessimento di RNFL, GCL, IPL e CT ($p<0.05$), mentre non vi erano differenze significative nella misurazione di RNFL e GCL tra micro- e macroadenoma ($p>0.05$). Tutti i pazienti presentavano differenze significative tra di loro riguardo la CT ($p<0.05$).

Questi risultati suggeriscono che in caso di tumori pituitari si verifica una degenerazione neurale, che può essere rappresentata dalla diminuzione del GCL negli stadi precoci, e con la progressione della patologia la degenrazione può interessare anche altri strati del GCC come RNFL e IPL.

RNFL e GCL sono risultati significativamente più sottili in tutti i pazienti a paragone con i soggetti di controllo. Nei tumori ipofisari, sia micro- che macroadenoma, nella valutazione dei dati oftalmologici bisognerebbe prendere in considerazione anche l'assottigliamento coroideo.

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