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ARTICLE

Assessment of inner retina layers thickness values in eyes with pituitary tumours before visual field defects occur

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Abstract

Background The purpose of this study was to evaluate macula, retinal nerve layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL) and macular nerve fibre layer (mNFL) thickness in patients with pituitary tumours who has normal visual field (VF).

Methods Thirty-five eyes of 35 patients with pituitary tumours with normal VF and 41 eyes of 41-healthy subjects were underwent a complete ophthalmic examination. The spectral domain- optical coherence tomography (OCT) was used to measure macular and optic disc parameters. Layer-by-layer segmentation was done automatically by using the new software. Data analyses were performed by using SPSS for Windows, version 22.0.

Results Average of total macula thickness inner temporal (p: 0.006), outer temporal ($p < 0.001$), inner nasal (p: 0.03), outer nasal (<0.001) were significantly lower in pituitary tumour group than normal group. Average of RNFL (p:0.009), temporal (p: 0.001), superiotemporal (p:0.004) and inferiotemporal (p: 0.01) were significantly lower in pituitary tumour group than normal group. Average of central GCL (p: 0.01) and central NFL (p: 0.03) were significantly lower in pituitary tumour group than normal group. There was no statistically significant difference between the two groups in IPL averages.

Conclusions Pituitary tumour patients with normal VF had reduced nasal and temporal section of the total macula, temporal RNFL, central mGCL and mNFL thicknesses, reflecting the corresponding to the anatomical substrate of the underlying pathology of chiasmal compression. This indicates that the presence of retinal thinning may be a sign of early detection of anterior visual pathway injury before VF loss becomes apparent.

Introduction

Pituitary tumours are common intracranial neoplasm and they constitute 15% of all intracranial neoplasms [1]. They are associated with endocrine system dysfunction, compression signs and symptoms by mass effect to the adjacent structures [2]. Compression of the optic chiasm can lead to loss of visual function by retrograde degeneration to retinal ganglion cells [3]. Neuro-ophthalmic pathologies can be seen as; loss of visual acuity, visual field (VF) defects and optic disc changes. Typically, damage of the crossed nerve fibres which are originating from temporal hemiretina, results with bitemporal hemianopia in the visual field test [4]. Routine screening of VF by automated perimetry is essential [5]. But the prevalence of VF defects in pituitary adenoma varies between 9 and 32% [6].

Optical coherence tomography (OCT) is a device that helps taking cross-sectional images of the retinal structure and quantifying the thickness of the macula layers noninvasively [7]. The macular ganglion cell complex (GCC) composes of the nerve fibre layer, the ganglion cell layer (GCL), and the inner plexiform layer (IPL) [8]. OCT can detect thinned macular GCC and retina nerve fibre layer (RNFL) which could be related with both optic neuropathies and chiasmal compression [7]. The new segmentation software designed for the spectral domain-OCT (SD-OCT) enables the independent quantification of all the retinal layers. The macular RNFL (mRNFL), macular ganglion cell layer (mGCL), and macular interplexiform layer (mIPL) can be measured separately. These three layers are the most affected by optic neuropathies. Previous studies have shown assessment of the optic nerve

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and macula thicknesses have been performed in patients with chiasmal compression [1, 2].

The purpose of this study is to evaluate macula, RNFL, mGCL, mIPL and macular nerve fibre layer (mNFL) thicknesses in patients with pituitary tumours who has normal VF. We researched whether OCT analysis could be used in neuro-ophthalmology units before VF defects developed.

Materials and methods

Declaration of Helsinki Principles were used, informed consent was confirmed by all participants and was approved by the Ethics Committee of Ankara Training and Researching Hospital. This study is a retrospective study. The consecutive patients with recently established diagnosis of pituitary tumours which had evidence with chiasm impingement at pituitary magnetic resonance images (MRI) with normal VF and who were consulted for neuro-ophthalmological examination before treatment at the Department of Ophthalmology of Ankara Training and Researching Hospital between 2016 and 2019 were enroled. Thirty-five eyes of 35 patients with pituitary tumours who had normal VF, underwent a complete ophthalmic examination. Best corrected visual acuity (BCVA) with LogMAR chart, slit lamp biomicroscopy, intraocular pressure (IOP) measurements with Goldmann applanation tonometer, dilated stereoscopic fundus examination, VF test and SD-OCT were examined.

The main inclusion criteria of the patients with pituitary tumour was evidence with chiasm impingement at pituitary MRI regardless of being macroadenoma or microadenoma. Subjects were excluded if they had myopia >6 diopters; a history of ocular surgery, any anterior segment, retinal, posterior segment or optic nerve disease other than compressive optic neuropathy, any previous radiotherapy or medical treatment because of pituitary adenoma, and if they had a history of diabetic or any other systemic diseases.

Forty-one eyes of 41-healthy participants without pituitary adenoma and with a normal ophthalmic examination were enroled as control group in the study. The inclusion criteria of normal individuals were; age >18 years, spherical refraction between +3.00 and −6.00 diopters, cylinder refraction within ±3.00 diopters and an IOP of <20 mm Hg. Exclusion criteria included history of ocular surgery, any anterior and posterior segment disease or optic nerve disease, including known glaucoma or optic nerve disease other than compressive optic neuropathy and a history of diabetic or any other systemic diseases.

The SD-OCT (Spectralis, Heidelberg, Germany; software version 6.0) was used to measure macular and optic disc parameters. All subjects were examined using the standard macula protocol of the OCT. Images had to have a quality index of at least 20 to be included in the study. The new software for the Spectralis OCT can perform layer-by-layer segmentation that includes: total retinal thickness, inner retinal layers, mRNFL, mGCL, mIPL, macular inner nuclear layer, macular outer plexiform layer, macular outer nuclear layer, photoreceptors, and retina pigment epithelium. The three layers in these nine zones were used in this study; mGCL, mIPL and mRNFL.

Early Treatment Diabetic Retinopathy Study (ETDRS) circle is the retinal thickness map analysis of the different layers for each of seven areas (Fig. 1). The circle consists of three rings; 1-mm (central), 3-mm (inner), and 6-mm (outer) diameter at the fovea. The inner and outer rings were then divided into four zones: superior, nasal, inferior, and temporal. Global macular volume for each layer also was recorded.

VF was performed using a Humphrey HFA II 750 automated field analyser (Humphrey-Zeiss Instruments, Dublin, CA). The 30-2 Swedish interactive threshold algorithm program was used. The VF reliability criteria included <20% fixation loss and <20% false negative and false positive rates. Perimetry was performed within 1 week of clinical examination and OCT measurements.

Patients were required to have a normal VFs result depending on absence of a temporal VF defect. Normal VF defined as none a cluster of three points with a probability <5% on the pattern deviation map, including at least one point with a probability of <1% or a cluster of two points with a probability of <1% with respect to the vertical meridian. All patients with a definite vertically demarcated temporal field loss in either eye on the pattern deviation map in VF were excluded.

Statistical analyses

Data analyses were performed by using SPSS for Windows, version 22.0 (SPSS Inc., Chicago, IL, United States). The distribution of continuous variables were determined by Kolmogorov Smirnov test. Levene test was used for the evaluation of homogeneity of variances. Continuous data were described as mean ± SD. Categorical data were described as number of cases (%). While the differences in normally distributed variables among more than two independent groups were analysed by one-way ANOVA. On the other hand, Kruskal Wallis test was applied for comparisons of the not normally data. When the p-value from one-way ANOVA or Kruskal Wallis test statistics were statistically significant, post hoc LSD or Conover's non-parametric multiple comparison test were used to know which group differs from others. It was evaluated degrees of relation between variables with pearson correlation or spearman correlation analysis. p-value < 0.05 was accepted as significant level on all statistical analysis.

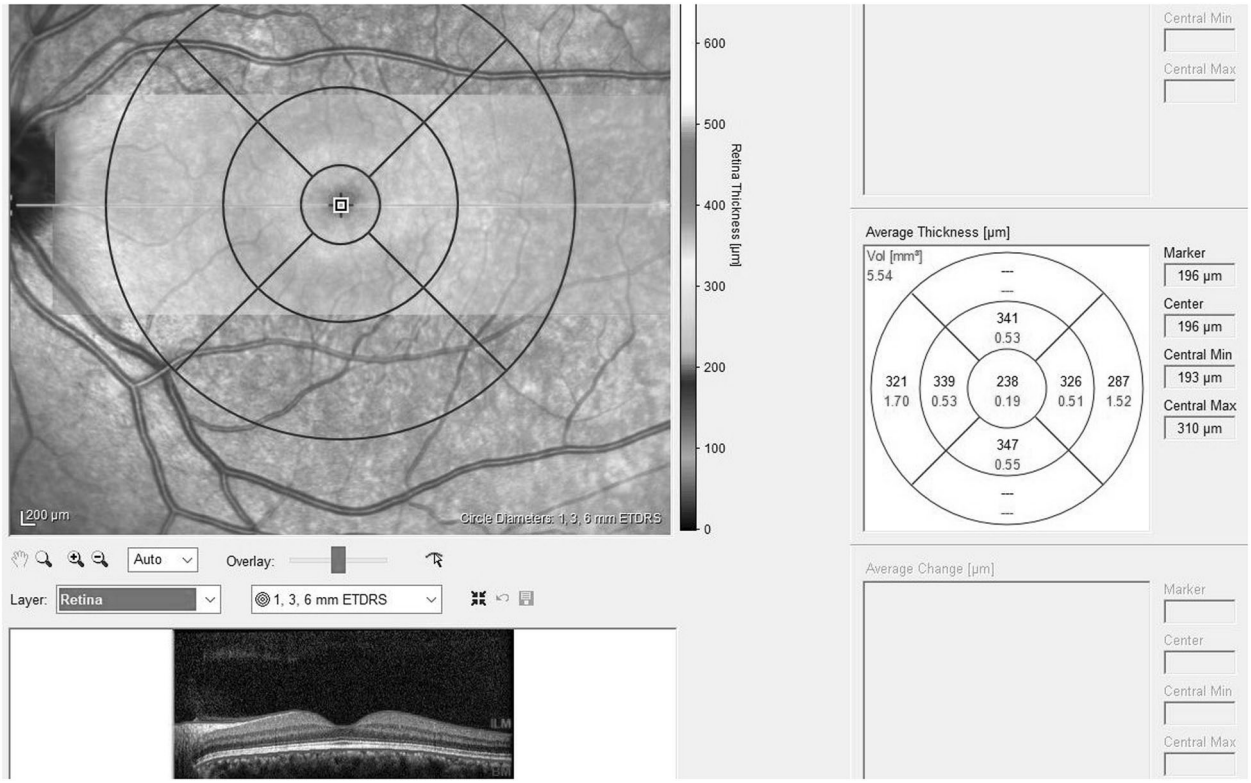

Fig. 1 The standard macula protocol of spectral domain optical coherence tomography (Spectralis, Heidelberg, Germany; software version 6.0) was used. Early Treatment Diabetic Retinopathy Study (ETDRS) circle is the retinal thickness map analysis of the different layers for each of seven areas. The circle consists of three rings; 1-mm, 3-mm, and 6-mm diameter at the fovea. The inner and outer rings were then divided into four zones: superior, nasal, inferior, and temporal. Global macular volume for each layer also was recorded. Layer-by-layer segmentation was done automatically by using the new software for the Spectralis OCT. The following macular measurements were described; inner retinal layers, mRNFL, mGCL, mIPL, macular inner nuclear layer, macular outer plexiform layer, macular outer nuclear layer, photoreceptors, and retina pigment epithelium.

Results

A total of 76 eyes of 76 participants divided in two groups. Thirty-five subjects in pituitary tumour group and 41 subjects in control group were analysed. The mean age of pituitary tumour group was 39.9 ± 12.7 years and normal group was 32.98 ± 7.41 years. BCVA, IOP were similar in patient and control groups. The general characteristics of subjects are shown in Table 1.

Average of the total macula thickness of inner temporal (p: 0.006), outer temporal ($p < 0.001$), inner nasal (p: 0.03) and outer nasal (<0.001) thickness were significantly lower in pituitary tumour group than normal group. Average of RNFL (p: 0.009), temporal (p: 0.001), superiotemporal (p:0.004) and inferiotemporal (p: 0.01) were significantly lower in pituitary tumour group than normal group. Average of central GCL (p: 0.01) and central NFL (p:0.03) were significantly lower in pituitary tumour group than normal group. There was no statistically significant difference between the two groups in IPL averages.

Table 1 Demographics of patients with pituitary tumour groups and control group.

	Pituitary tumour group (n: 33)	Control group (n: 41)	p
Gender, male	8/22.8%	18/41.9%	0.048
Age, year	33.50 ± 11.2	32.98 ± 7.41	>0.05
BCVA, LogMAR	0.03 (0–1)	0	>0.05
IOP, mm Hg	12.90 ± 3.22	13.22 ± 5.10	>0.05

BCVA best corrected visual acuity, *IOP* introcular pressure.

Macular segmentation, optic disc and macular thickness analysis were summarized in Tables 2 and 3.

Discussion

The GCL accounts for up to 40% of the thickness in the macular area. The macular thickness can point to possible ganglion cell loss. These structures that could be measured by OCT has been accepted as useful diagnostic value for

Table 2 Comparison of macula and retina nerve fibre layer of optic disc thicknesses between eyes with pituitary tumour group and control group.

	Pituitary tumour group	Control group	*p* value
Macula centre	263.66	265.11	0.77
Macula inner temporal	333.12	343.48	0.006*
Macula outer temporal	297.75	319.27	<0.001*
Macula inferior	336.06	340.13	0.38
Macula inner nasal	336.39	339.74	0.03*
Macula outer nasal	307.06	320.45	<0.001*
Makula superior	341.51	341.76	0.95
RSLT mean	95.48	103.32	0.009*
RSLT temporal	67	76.53	0.001*
RSLT superiotemporal	115.27	143	0.004*
RSLT inferiotemporal	138.45	151.59	0.01*
RSLT inferionasal	121.06	111.76	0.11
RSLT nasal	73.48	77.39	0.19
RSLT superionasal	115.27	110.04	0.27

RSLT retina nerve layer thickness of optic disc.

*$p < 0.05$.

chiasmal damage [7]. In previous studies, patients with chiasmal compression showed significant thinning of the retinal thickness on the nasal macular area, which were associated with the severity of VF damage [9, 10]. The thickness of nasal hemi-retina in these patients predominantly depends on damaging of the crossed fibres. Our study demonstrated that the temporal macular thickness was significantly lower as well as the nasal macular thickness in pituitary tumour group before VF defect occurs. The macular thickness measurements may be used as an indicator of neuronal loss and could clinically prove the damage caused by pituitary tumour.

Monterio et al. [11] reported that average RNFL thickness is the most frequently abnormal parameter in eyes with band atrophy (BA) caused by chiasmal compression. The other studies also have demonstrated that temporal sides of RNFL thickness reduction is correlated with bitemporal hemianopia defect [10, 12, 13]. Danesh-Meyer et al. suggested that patients with RNFL thinning had more severe VF defects even they had good visual acuity. And they suggested RNFL measurement was the prespecified marker for axonal loss in chiasmal compression [14, 15]. Our results also suggest that total and temporal side of RNFL were significantly lower in patients with pituitary tumour even if they had normal VF. This findings confirm the anatomical architecture of the crossing nerve fibres in human eyes.

Table 3 Comparison of inner retinal layer thickness between eyes with pituitary tumour group and control group.

	Pituitary adenoma group	Control group	*p* value
GCL centre	15.48	17.45	0.01*
GCL inner temporal	52.33	52.88	0.68
GCL outer temporal	40.12	40.67	0.57
GCL inferior	51.33	53.44	0.17
GCL inner nasal	47.6	48.72	0.41
GCL outer nasal	38.51	38.18	0.49
GCL superior	53	53.76	0.54
NFL centre	11.81	13.16	0.03*
NFL inner temporal	21.54	21.32	0.74
NFL outer temporal	46.48	47.76	0.45
NFL inferior	25.15	25.46	0.78
NFL inner nasal	17.03	17.34	0.35
NFL outer nasal	17.54	17.69	0.67
NFL superior	24.27	24.6	0.7
IPL centre	20.54	20.55	0.99
IPL inner temporal	42.09	67.42	0.38
IPL outer temporal	30.87	31.6	0.45
IPL inferior	40.09	41.95	0.08
IPL inner nasal	40.42	41.58	0.19
IPL outer nasal	33.18	34.04	0.3
IPL superior	41.18	42.34	0.21

GCL ganglion cell layer, *NFL* nerve fibre layer, *IPL* inner plexiform layer.

*$p < 0.05$.

GCC parameters is useful in evaluating structural damage in patients with chiasmal compression [4, 14]. Akashi et al. [8] demonstrated that the inner macular parameters in the nasal hemiretina had significantly higher diagnostic ability to detect BA in chiasmal compression. Tan et al. [6] also suggested that the GCC map could be correlated with VF defects. Also, in another study, 75% of 12 eyes with temporal VF depression had significant decrease in GCC thickness, predominantly in the nasal hemi-retina [14]. Those studies included pituitary tumour patients with temporal hemianopsia. But also, there are recently published studies which demonstrate thinning of inner retina layers with normal VF in pituitary tumours. Zhang et al. [16] found thinner GCL in pituitary non-functional adenoma with chiasm compression patients without VF defect. Likewise, Tieger et al. [17] studied twenty-three patients with chiasmal compression, six patients had no VF defect and these patients showed

statistically significant loss of GCC compared with control group. Blanch et al. studied with seven sellar tumour patients with normal visual function but no evidence of compressive chiasmopathy in MRI. They suggested that GCC analysis is more sensitive than VF testing with standard automated perimetry in the detection of compressive chiasmopathy or optic neuropathy [2]. In Lee et al. study [18], eyes with chiasmal compression showed thinning of the macular RNFL, GCL, IPL in patients with partial to no recovery of VF after tumour excision. In another study, 12 pituitary adenoma patients who had optic chiasmal compression without VF defect, had found significantly thinner mGCIPL in the superior, superonasal, inferonasal, and inferior sectors [19]. Similar to these studies, we found central mGCL and central mNFL thicknesses were significantly lower in pituitary tumour patients who had normal VF test. Our results suggest that mGCL and mNFL may be useful for early detection of optic neuropathy caused by pituitary tumours.

In conclusion, patients with pituitary tumour had thinner nasal and temporal macula, temporal RNFL, central mGCL and mNFL layers before VF defects developed. In addition, these results may be accepted to be showing that OCT is clinically useful for detecting damage of optic nerve when VF testing is unreliable.

Thus, we may say that nasal macular, temporal RNFL, central mGCL and mNFL measurements can be used as a diagnostic test for patients with pituitary tumours. However, inevitably both VF and OCT examinations remain important at detecting damage due to pituitary tumours.

Summary

What was known before

- Pituitary tumours cause thinner ganglion cell complex, retina nerve fibre layer, macula

What this study adds

- Retina nerve fibre layer, ganglion cell layer and macular nerve fibre layer can be thinner in pituitary adenoma with normal visual field.
- These parameters may be diagnostic value for pituitary adenoma, especially visual field test is unreliable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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