PITUITARY ADENOMA- VISUAL FIELDS, RETINAL NERVE FIBRE LAYER AND GANGLION CELL-INNER PLEXIFORM LAYER THICKNESS ANALYSIS- A CORRELATIONAL STUDY

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ABSTRACT

BACKGROUND

Pituitary adenoma is a benign and most common tumour of the pituitary gland. It is also the most common parachiasmal tumour and accounts for approximately 10-15% of primary intracranial neoplasms. It has an annual incidence rate of 0.8–8 per 1,00,000 population. Pituitary adenomas are classified as functional and non-functional based on their hormonal activity. Functional adenomas are usually detected earlier due to clinical manifestations produced by excess of hormones.

The aim of the study is to analyse visual acuity, visual fields, RNFL thickness and GCIPL thickness on optical coherence tomography (OCT) and to find a correlation between these parameters and tumour volume in patients diagnosed with pituitary adenoma.

MATERIALS AND METHODS

48 patients diagnosed with pituitary adenoma confirmed by MRI scan underwent complete ophthalmic evaluation (visual acuity, slit-lamp examination, fundus evaluation), perimetry using 30-2 SITA FAST strategy, (Humphrey Field Analyzer; Carl-Zeiss Meditec, Dublin, CA), and OCT of disc (for retinal nerve fibre layer- RNFL thickness) and macula (for ganglion cell-inner plexiform layer (GCIPL) thickness) using Cirrus HD-OCT (Carl Zeiss Meditec, Dublin, CA) at Bangalore West Lions Super Speciality Eye Hospital, between June 2014 to June 2016. Various parameters like Mean Deviation (MD), Pattern Standard Deviation (PSD) and RNFL and GCIPL thickness on OCT were analysed and correlated with each other.

RESULTS

Mean tumour volume in patients was $12.26 \pm 15.8 \text{ cm}^3$. Most of the patients had visual acuity 6/18 or better. Bitemporal hemianopia was seen in only 5 (12.2%) patients. Superotemporal quadrantanopia, arcuate defects, tubular fields and homonymous hemianopia were the other field defects seen. Total and pattern deviation plot of visual fields correlated well with tumour volume and visual acuity. On visual field analysis, the MD (-8.18 ± 8.65 dB) was depressed compared to the control group (-2.0 ± 1.8 dB), and PSD value (5.76 ± 4.8 dB) was higher than controls (1.9 ± 1.0 dB). However, MD and PSD did not correlate well with tumour volumes. Mean RNFL thickness (85.9 ± 14.5 µm) and mean GCIPL thickness (71.6 ± 17.2 µm), values revealed global thinning in patients when compared with RNFL thickness (92.4 ±7.6 µm) and GCIPL thickness (80.4 ± 4.0 µm) in controls. MD and PSD correlated well with all sectors of RNFL and GCIPL (p value <0.01).

CONCLUSION

PSD and GCIPL were concluded to be valuable tools in prognosis of the disease. Our study reinforces the effectiveness of investigations like standard automated perimetry and OCT in prognosticating the neurological disorder like pituitary adenoma and to understand the structural and functional relationship of the disease process. Our study recommends the use of GCIPL thickness evaluation by OCT for patients with unreliable fields or fields not corresponding to the disease progress.

KEYWORDS

Pituitary Adenoma, Optical Coherence Tomography (OCT), Visual Fields, MD, PSD, Bitemporal Hemianopia, RNFL, GCIPL.

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BACKGROUND

Pituitary adenoma is a benign and most common tumour of the pituitary gland. It is also the most common parachiasmal tumour and accounts for approximately 10-15% of primary intracranial neoplasms.^{1,2} It has an annual incidence rate of 0.8–8 per 1,00,000 population.³ Pituitary adenomas are classified as functional and non-functional based on their hormonal activity. Functional adenomas are usually detected earlier due to clinical manifestations produced by excess of hormones. Most non-functional adenomas may go

unrecognised in early stages. However, as they gradually progress, pressure effects of the enlarging tumour on the visual pathways cause ocular manifestations.⁴

Clinically, they may present as infertility, acromegaly/gigantism, or amenorrhoea galactorrhoea syndrome, etc. Most common ocular manifestations are visual field defects and diminution of visual acuity.⁵

Standard automated perimetry helps in analysing the visual field defects. Bitemporal field defect is the most common visual abnormality seen in pituitary adenoma. The size and relation of the tumour to the visual pathway affects the changes seen in the visual field.^{5,6}

The tumour size is accurately obtained using MRI. Based on size of the tumour, the adenomas are classified either as microadenomas (less than 1 cm) or macroadenomas (more than 1 cm). Macroadenomas usually manifest clinically due to their compressive effect on adjacent structures, most importantly the optic chiasm.

Various studies have suggested that retinal thinning, mainly that of Retinal Nerve Fibre layer (RNFL), Ganglion Cell layer (GCL) and Inner Plexiform Layer (IPL) is significantly associated with chiasmal compression. In pituitary adenoma, the RNFL thinning is more pronounced in the temporal and nasal disc sectors, whereas GC-IPL (together known as ganglion cell-inner plexiform layer) thinning mainly is noted in the nasal sectors of macula. Optical coherence tomography (OCT) is used to analyse the thickness of the RNFL at the disc and GC-IPL thickness at the macula.

The visual field changes and thinning of retinal layers are related to the size of the tumour. This study intends to find if any significant correlation exists between the parameters mainly visual acuity, tumour volume, visual fields and OCT. This study also aims at exploring if any prognostic significance can be assigned to these tests, either individually or in relation to each other.

MATERIALS AND METHODS

The study was conducted at the Outpatient Department of Bangalore West Lions Super Speciality Eye Hospital, Bangalore. Patients diagnosed with pituitary adenoma confirmed by MRI, referred from NIMHANS hospital to our hospital were included. It was a Prospective, Analytical, cross sectional study. 48 patients were taken up for the study over a period of two years (June 2014-June 2016). We excluded patients with other cranial tumours, patients with coexisting cataract/glaucoma, patients with recurrence of tumour following previous surgery and patients too ill to allow adequate visual field examination.

The research followed institutional guidelines and the tenets of the World Medical Association, Declaration of Helsinki. The study was approved by the ethics committee of our institute. Informed consent was obtained from all the patients included in the study.

All the patients presenting to the Outpatient Department with the diagnosis of pituitary adenoma (confirmed on MRI) and the age-matched control group underwent a detailed evaluation. Particulars of the patient were noted including age, gender, tumour dimensions according to MRI Reports (tumour volume was calculated based on Cavalieri's principle using formula $4/3\pi$ ($a/2 \times b/2 \times c/2$) (where a, b, and c represent the diameters in the three dimensions). History of medical and ocular symptoms was taken. A detailed ophthalmic examination was done which included, Best corrected visual acuity, and near vision, Anterior segment examination on slit-lamp, Extraocular movements and colour vision (Ishihara's chart), Intraocular pressure measurement (Perkin's tonometry), Indirect ophthalmoscopy for fundus examination. Visual field testing was done using standard automated perimetry with 30-2 SITA FAST strategy, (Humphrey Field Analyzer; Carl-Zeiss Meditec, Dublin, CA), with Goldmann size III target. Near refractive correction was used, calculated according to the subjects' age by the perimeter software. Reliability criteria were false positives, false negatives, or fixation losses less than 33%. Ocular coherence tomography (OCT with dilated pupils was done using OCT scanner (Cirrus; Carl Zeiss Meditec, Dublin, CA). Good-quality scans had to have focused images and signal strength equal to or higher than 7 and a ring centred around the optic disc in the case of the RNFL scans. For macula scans, the radial scans had to be centred on the fovea. RNFL algorithm (Cirrus-OCT; Carl Zeiss Meditec) was used to obtain RNFL thickness measurements. Two images were acquired from each subject, with each image consisting of a 3.4-mm diameter ring around the optic disc. Peri-papillary RNFL thickness parameters including average thickness (360°); temporal, superior, nasal, and inferior quadrant were obtained. Macular thickness parameters were divided in to 6 sectors I to VI clockwise in right eye and anticlockwise in left eye. Average thickness of GCIPL along with individual thickness of each sector was obtained. Signal strength of 7 or above was accepted.

The vision (BCVA) and MRI tumour volume was correlated with each other and also with other parameters like MD, PSD in visual fields and RNFL and GCIPL in OCT.

Control group patients were identified from general ophthalmology clinic based on age. After slit-lamp biomicroscopy those who were ruled out to have any ocular and systemic pathologies were subjected to visual fields test and OCT imaging. Controls and patients were compared in terms of MD, PSD, RNFL and GCIPL and results were analysed.

Methods of Statistical Analysis-

Descriptive and inferential statistical analysis was carried out in the present study. Results of continuous measurements are presented in Mean \pm SD (range-min/max) and results on categorical measurements are presented in number (%). Significance was assessed at 5% level of significance. The Pearson correlation coefficient was used to evaluate any correlation between two continuous variables. Spearman coefficient of correlation was used to correlate two nonparametric variables. Also, Mann-Whitney U test and a twotailed Chi square test was used to find the significance of study parameters on categorical scale between two or more groups and a p value of <0.05 was considered as significant for measured variables. P value <0.01 was considered strongly significant. R value above 0.5 indicated dependency with positive correlation and above -0.5 showed dependency with negative correlation.

RESULTS

This study includes 48 patients referred from NIMHANS to our hospital.

Most of the patients were in age group 30 to 50 years. Most of the patients (85.4%) had a tumour volume of <25 cubic cm. Most of the patients (27) did not have any significant medical history. 4 patients complained of headache, 2 had thyroid abnormalities, 4 had acromegalic features, 9 suffered from hypertension and 10 were diabetic.

Patients and controls underwent ophthalmic evaluation and investigations of both eyes, however, for statistical convenience only one eye per patient (which according to visual field parameter was more affected) was taken for data analysis. Most of the patients (77%) had visual acuity better than 6/18. Only 2 (4.8%) patients had no perception of light.

Visual Fields

A) Pattern of Visual field Changes

Visual fields could not be done due to poor vision in the worse eye, in 6 patients. In all calculations for visual fields and OCT, those patients have been excluded making the total number of patients 42. Hence, number of controls taken was also 42.

When we studied visual fields of all the eyes, 22 (52.8%) patients had no field defect. 6 (14.2%) patients had superior quadrantanopia, 8 (19.2%) had temporal hemianopia. Arcuate defect was seen in 1 (2.4%), tubular fields in 3 (7.2%) and generalised depression in 2 (4.8%) patients. When total and pattern deviation plot bilateral effect of the tumour on visual fields it was observed that 5 (12%) patients of 42 had bitemporal hemianopia, 1 (2.4%) patient had bilateral superior defects, similarly tubular field defect in both eyes and superior temporal quadrantanopias in both eyes were seen in only 1 (2.4%) patients.

B) Mean Deviation (MD) and Pattern Standard Deviation (PSD)

Most of the patients i.e. 28 (67.2%) had a reduction in MD of less than 10 dB. Average visual field MD value was -8.18 \pm 8.65 dB which was worse than that of the control group (Table 1). A PSD value below 5 dB was seen in 26 (62%) patients. Average visual field PSD value was 5.26 \pm 4.87 dB which was higher than that of the control group. P value was significant at <0.05 for both MD and PSD using Mann-Whitney U test. (Table 1.)

RNFL Thickness and GCIPL Thickness

RNFL thickness of nasal (64.36 ± 14.3 µm) and temporal (57.04 ± 13.0 µm) sectors was lesser in patients when compared to superior (106.84 ± 27.1 µm) and inferior (117.7 ± 25.1 µm) sectors, with temporal being thinner than nasal sector (Table 2 and Figure 3).

On comparing the GCIPL sector thickness at macula, inferonasal and inferior sectors are thinner in comparison to rest of the sectors. (Table 3 and Figure 4).

Spearman Correlation was used to compare the RNFL and GCIPL sectors with respect to MD and PSD. All RNFL and GCIPL sectors correlated strongly with MD and PSD with a p value <0.01.

Mean RNFL thickness in patients was lower when compared to controls ($85.9 \pm 14.5 \mu m vs.$ Mean $\pm SD = 92.4 \pm 7.6 \mu m$). Mean GCIPL thickness in patients was 71.6 \pm 17.2 μm which was also less when compared to controls (Mean $\pm SD = 80.4 \pm 4.0 \mu m$). (Table 4 and Figure 5).

Hence, both mean RNFL thickness and GCIPL thickness at disc and macula are respectively reduced in patients with pituitary adenoma when compared to normal.

A positive correlation was seen on correlating MD with RNFL thickness and GCIPL thickness in the patient group (Figure 6).

PSD values are negatively correlated to RNFL and GCIPL indicating a high PSD value would show thinning of RNFL and GCIPL (Figure 6).

Average RNFL thickness correlates well with both MD and PSD. Nasal sectors of GCIPL show a very strong correlation to both MD and PSD.

Correlation of MD and PSD with RNFL thickness and GCIPL thickness is based on colour coding of the RNFL and GCIPL thickness map.

Most of the patients having MD less than 10 dB had a normal thickness of RNFL represented by green on colour coded RNFL thickness map. Patients with MD more than 10 dB show thinner RNFL (represented by yellow or red on colour coded RNFL thickness map) p < 0.05. Similarly, most of the patients having a MD less than 10 dB had normal thickness of GCIPL. Patients with MD more than 10 dB show thinner GCIPL p < 0.05. In our study, GCIPL thinning was also seen in MD below 10 dB indicating GCIPL analysis to be a vital tool in prognosis of the disease. Similar correlation was seen with PSD values less than 10 dB having thicker RNFL and GCIPL and those with values more than 10 dB showing thinner RNFL and GCIPL, p < 0.01.

But GCIPL thinning was appreciably noticed even in PSD values less than 5 dB indicating early changes in GCIPL layer in the disease. This also implies a better and early detection of neuro-ophthalmic disorder by GCIPL thickness analysis (p value 0.002) when compared to RNFL thickness analysis (p value 0.007).

PSD values show a more significant (p<0.01) relation than MD (p<0.05) with both average RNFL and average GCIPL making PSD a more sensitive tool of investigation in this disease. Spearman correlation was used to correlate RNFL sectors with corresponding GCIPL sectors. All values had p<0.05 and correlation coefficient of all these individual sectors and averages were depicted in Table 5 and Figure 7 (Pearson correlation coefficient with R=0.617 and p value <0.05 shows a positive correlation). It is observed that all RNFL sectors correlated with their respective GCIPL sectors, p value <0.05. A spearman correlation between average RNFL and average GCIPL was very high 0.677. Nasal sector

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(2, 3) of GCIPL strongly correlated with average RNFL (r=0.803). Inferior and nasal sector of GCIPL (2, 3, 4) correlated maximum with respect to most sectors in RNFL in general.

Most of the patients were with tumour volume less than 25 cm³, BCVA better than 6/18. Tumour volume and MD of visual fields show a Pearson correlation coefficient R = -0.127 had hence negatively correlated, but the association was not significant at 0.422 (>0.05). Tumour volume and PSD correlated positively with Pearson correlation coefficient R =0.11, however p value at 0.47 (>0.05). With Chi square value of 41.1, and p value<0.01, significant relationship existed between tumour volume and average thickness of RNFL and average thickness of GCIPL.

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Figure 1. RNFL Tomogram Sector Wise



Figure 2. Ganglion Cell Analysis



Figure 3. Mean RNFL Thickness at Disc



Figure 4. GCIPL Thickness at Macula



Figure 5. RNFL and GCIPL in Patients and Controls



Figure 6. Visual Field Parameters in Relation to OCT Parameters



Figure 7. Linear Regression Plot of Average RNFL and Average GCIPL

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	MD	MD (Control)	PSD	PSD (Control)	
Mean	-8.18	-2.0	5.76	1.9	
Standard Deviation	±8.65	±1.8	±4.9	±1.0	
Range	27.74	7.1	15.2	5.0	
Minimum	-27.9	-6.4	1.31	1.2	
Maximum	-0.16	0.7	16.5	6.2	
Count	42	42	42	42	
Table 1. Comparison of MD and DSD of Patients with Controls					

Table 1. Comparison of MD and PSD of Patients with Controls

RNFL	Range	Minimum	Maximum	Mean (µm)	Std. Deviation
SUP	110	54	164	106.84	27.122
INF	105	55	160	111.73	25.149
TEM	52	34	86	57.04	13.028
NAS	92	12	104	64.36	14.274
AVG	59	53	112	85.17	15.786
Table 2 Description of PNEL Thickness Sector Wise					

Table 2. Description of RNFL Thickness Sector Wise

GCIPL	Range	Minimum	Maximum	Mean	Std. Deviation
GCIPL 1 (S)	88	10	98	70.8	19.05
GCIPL 2 (SN)	86	10	96	71.8	18.24
GCIPL 3 (IN)	63	34	97	69.22	18.016
GCIPL 4 (I)	68	26	94	68.46	17.114
GCIPL 5 (IT)	73	24	97	71.76	18.334
GCIPL 6 (ST)	75	22	97	70.87	17.823
GCIPL AVG	64.0	32.0	96.0	71.563	17.2435
Table 3. Description of GCIPL Thickness Sector Wise					

	RNFL (Average)	RNFL (Average) - Control	GCIPL (Average)	GCIPL (Average) Control	
Mean	85.9	92.4	71.6	80.4	
Standard	+14 5	+7.6	+17.2	+4.0	
Deviation	T14.2	17:0	117.2	±4.0	
Range	56.0	18.0	55.0	16.0	
Minimum	56	88.0	32.0	75.0	
Maximum	112	106.0	96.0	91.0	
Count	46	42	46	42	
Table 4. Comparison of Average DNEL and Average CCIDL Comparison of Study and Control Crown					

 Table 4. Comparison of Average RNFL and Average GCIPL Comparison of Study and Control Group

RNFL	GCIPL 1 (S)	GCIPL 2 (SN)	GCIPL 3 (IN)	GCIPL 4 (I)	GCIPL 5 (IT)	GCIPL 6 (ST)	AVG
SUP	0.522	0.69	0.71	0.570	0.527	0.530	0.625
INF	0.583	0.683	0.647	0.585	0.561	0.565	0.647
TEM	0.494	0.557	0.467	0.4	0.421	0.480	0.464
NAS	0.497	0.474	0.619	0.566	0.421	0.483	0.546
AVG	0.645	0.759	0.803	0.689	0.6	0.615	0.677
Table 5. RNFL Sectors Correlated to GCIPL Sectors (Spearman Correlation Coefficient)							

DISCUSSION

In our study, 12.2% of eyes showed bitemporal hemianopia. Superotemporal quadrantanopia, arcuate defects, tubular fields and homonymous hemianopia were the other field defects seen. Similar findings were seen by Meenakshi Y. D et al.⁵ Bitemporal hemianopia was the predominant field defect in a similar study by Jung Pil Lee et al.⁷ Bitemporal hemianopia could not be demonstrated to be most common field defect in our study. The probable reason might be that some patients were already on medical treatment for the tumour that might have contributed to regression of the defect. Lesions that damage the body of the optic chiasma

characteristically produce bitemporal hemianopia. In prefixed chiasma, optic tract gets affected first, producing a homonymous hemianopic pattern of VF loss. In a postfixed chiasma, either one of the optic nerves may be affected more with a worse visual field defect of one eye and an altitudinal pattern. Superior arcuate field defect can occur with a postfixed chiasma as an optic nerve rather than chiasma lies over the sella tursica.⁵ Jung Pil Lee et al ⁷ also found unilateral temporal hemianopic changes and unilateral superotemporal quadrantanopias. With this finding they emphasised that neuroimaging is necessary in patients presenting even with uniocular hemianopic field defects. To quantify VF defects, we used the MD and PSD values of Humphrey perimeter. MD provides useful information concerning overall abnormality of a single field, as well as information regarding the worsening or improvement of fields over time. PSD shows the pattern of a localised abnormality.7 Both of the parameters are expressed numerically, so those are useful to quantify the VF defects more accurately.MD and PSD values obtained from the automated perimetry chart showed significant difference when compared to controls. MD was worse than that in the control group (-8.18 \pm 8.65 dB vs. -2.0 \pm 1.8 dB) and PSD values were higher than controls (5.76 \pm 4.8 dB vs. 1.9 \pm 1.0 dB). Sansal Gredik et al⁸ in their study found similar results (MD -5.15 ± 5.38 and PSD 4.55 ± 4.26 vs. MD -1.73 \pm 1.5 dB and PSD 1.5 \pm 0.7 dB in the patient and control group respectively). Chan Hee Moon et al⁹ found that in patients the preoperative MD was -16.75 ± 9.04 and PSD 9.59 ± 4.62 which was significantly lesser than that of the control group.

In our study, peripapillary RNFL thickness and GCIPL thickness at macula were estimated using Cirrus HD-OCT. Mean RNFL in our study was significantly lesser when compared to controls. Similarly, mean GCIPL thickness of patient group was lesser than that of the control group. Recent studies have carried out morphologic assessments of the optic nerve and retina in patients with chiasmal compression with similar results.10 An OCT analysis of circumpapillary RNFL thickness by OCT can detect not only the characteristic circumpapillary RNFL loss corresponding to band atrophy of the optic disc in eyes with chiasmal compression, but also the correlation between the degree of circumpapillary RNFL loss and the amount of visual field ${\rm loss.^{10}}\,{\rm MD}$ in our study showed a positive correlation with RNFL thickness and GCIPL thickness implying more thinning with a higher MD. PSD values are negatively correlated to RNFL thickness and GCIPL thickness implying that high PSD values would show thinner RNFL and GCIPL layers.

Average RNFL thickness in the patient group, correlated well with both MD and PSD. Nasal sectors of GCIPL (2, 3) show a very strong correlation to both MD and PSD. Helen V. Danesh-Meyer et al¹¹ in their study also correlated the fields (MD and PSD) and RNFL parameters. Their results show good correlation of MD and PSD with average RNFL thickness. Also Chan Hee Moon et al¹² found a good correlation between average GCIPL thickness with MD.

With stronger correlation of PSD (p < 0.01) values than MD (p<0.05) with OCT parameters, we inferred that PSD is a more sensitive tool of investigation while evaluating patients with pituitary adenoma.

Even with MD of less than 2 dB and PSD values below 5 dB, severe thinning of GCIPL layer was noted in our study group, implying that GCIPL thickness analysis is a better tool than RNFL thickness analysis.

In our study, all RNFL sectors correlated very well with corresponding GCIPL sectors (p<0.05). We observed that there was a high correlation between average RNFL thickness and average GCIPL thickness in the patient group. Nasal sectors (2, 3) of GCIPL strongly correlated with

average RNFL. Inferior and nasal sector of GCIPL (2, 3, 4) correlated maximum with respect to most sectors in RNFL in general. However, Mário Monteiro et al¹³ in their study found significant correlation between the nasal, temporal and average macular (GCIPL) thickness with temporal sectors of RNFL (<0.01) in pituitary adenoma patients.

When we used colour coding of RNFL and GCIPL thickness maps on OCT to classify RNFL thickness in the study group, we found a significant correlation between tumour volume and average RNFL and average GCIPL thickness.

CONCLUSION

Visual fields (MD and PSD) and OCT (RNFL thickness and GCIPL thickness) were all found to be valuable investigations individually and in correlation to each other in investigation of pituitary adenoma.

 PSD was concluded to be a more sensitive parameter than MD.

GCIPL thickness showed good prognostic significance when compared to RNFL thickness in the disease process.

In cases of unreliable fields report or reports not corresponding to disease progress, an ophthalmologist should consider retinal thickness parameters especially GCIPL thickness at macula for prognosticating the disease.

Thus, our study reinforces the effectiveness of OCT for prognosticating the neurological disorder like pituitary adenoma and to understand the structural and functional relationship of the disease process.

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