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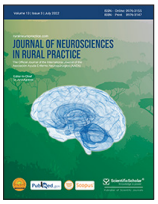

Original Article

Retinal nerve fiber layer thickness and its correlation with visual symptoms and radiological features in pituitary macroadenoma

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ABSTRACT

Objective: The aim of the study was to evaluate the association of the thickness of retinal nerve fiber layer (RNFL) with (i) visual symptoms and (ii) suprasellar extension defined by magnetic resonance imaging (MRI) in patients with pituitary macroadenoma.

Materials and Methods: RNFL thickness of 50 consecutive patients operated for pituitary macroadenoma between July 2019 and April 2021 were compared with standard visual examination findings and MRI measurements such as optic chiasm height, distance between the optic chiasm and adenoma, suprasellar extension, and chiasmal lift.

Results: The study group included 100 eyes of 50 patients operated for pituitary adenomas with suprasellar extension. RNFL thinning predominantly involved the nasal (84.26 ± 16.43 μm) and temporal quadrants (70.72 ± 14.80 μm) and correlated well with the visual field deficit ($P < 0.001$). Patients with moderate-to-severe deficit in visual acuity had a mean RNFL thickness <85 μm and patients with severe disc pallor had extremely thin RNFLs (<70 μm). Suprasellar extension defined as Wilsons Grade C, D, and E and Fujimotos Grades 3 and 4 were significantly associated with thin RNFLs <85 μm ($P < 0.01$). Chiasmal lift more than 1 cm and tumor chiasm distance of <0.5 mm were associated with thin RNFL ($P < 0.002$).

Conclusion: RNFL thinning correlates directly with the severity of visual deficits in patients with pituitary adenoma. Wilsons Grade D and E, Fujimoto Grade 3 and 4, chiasmal lift more than 1 cm, and chiasm tumor distance <0.5 mm are strong predictors of RNFL thinning and poor vision. Pituitary macro adenoma and other suprasellar tumors need to be excluded in patients with preserved vision but having obvious RNFL thinning.

Keywords: Retinal nerve fiber layer, Pituitary adenoma, Optical coherence tomography

INTRODUCTION

Conventionally, objective assessment and quantification of visual involvement in sellar suprasellar tumors are done using visual acuity (VA), visual field (VF), and optic disc evaluation.[1-3] Optical coherence tomography (OCT) is a new investigative modality which can indirectly measure the compressive effect of sellar-suprasellar tumors on the visual pathway.[4,5] Long standing compression of the visual pathway will cause progressive loss of ganglion cell axons and retinal nerve fiber which will be seen as retinal nerve fiber layer (RNFL) thinning. OCT provides a quantitative estimate of the RNFL thinning and thus provides a valuable prognostic tool.[6,7] However, it is often found that RNFL thinning does not always correspond to visual deficits and to the radiological extent of chiasmal compression.[8,9] Studies have attempted to correlate VA and VF with OCT and radiological features of chiasmal compression and found them to be inconsistent and variable.[10-12] This study attempts to analyze the correlation between RNFL thickness and VA, VF, and optic disc pallor in patients with pituitary adenoma. We have additionally analyzed the influence of magnetic resonance imaging (MRI) findings of chiasmal compression on RNFL thickness.

MATERIALS AND METHODS

The study was conducted jointly by the Department of Neurosurgery and Ophthalmology and after appropriate approvals from the Institutional Ethics Board (IEC 29/2019). Written informed consent was obtained from all the patients. All consecutive patients with sellar suprasellar tumors managed in the department of neurosurgery between July 2019 and April 2021 were included in the study. The inclusion criteria were as follows: (1) Patients having MRI confirmed pituitary macroadenoma with suprasellar extension and (2) no other associated central nervous system or ophthalmological pathology which can affect vision.

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VA was evaluated using the Snellen chart. Pre-operative visual function was classified into four categories: Normal (6/6 with normal VF); mildly impaired (6/9 to <6/18 with or without VF deficits); moderately impaired (6/18 to <6/60); and severely impaired (6/60 or worse).

VF was measured using automated Goldmann perimetry. VF involvement was graded as: Mild (field defect involving only one quadrant/A generalized constriction of field <20%); moderate (field defect involving two quadrants as in temporal hemianopia/a generalized constriction 20–40%); and severe (defect involving three or more quadrants-to severe constriction like tubular fields or when VA was very poor and a field could not be done).

Optic disc pallor was evaluated by ophthalmoscopy using 90D lens and slit-lamp and recorded as: Normal; mild (Early/doubtful temporal pallor); moderate (definite temporal disc pallor); and severe (nasal and temporal/Total disc pallor as in optic atrophy).

OCT

RNFL thickness was analyzed with spectral domain OCT (SD-OCT), a form of low-coherence interferometer using infrared light. Retinal tissue scan using SD-OCT was done at a speed of 25,000–70,000 A-scans per second with axial resolution of 3–5 microns and transverse resolution of 12–20 microns. An ophthalmoscope was used to capture Fundus surface images at a wavelength of 785 nm. Cross-sectional images of the retina were captured using an infrared light source with a wavelength of 880 nm. OCT image capture mode was optic disc cube 200 × 200, a disc circle mode with reference zone of 3.46 mm diameter in the peripapillary retina with 1024 scans in this area. RNFL thickness was represented as Temporal-Superior-Nasal-Inferior-Temporal graph measured by parapapillary circles of A-scans which gave a color-coded distribution of normal value according to patient's age compared to the normative database of the SD-OCT system. Mean RNFL thickness values of the nasal, temporal, superior, and inferior quadrants in micrometers with color-coded representation in comparison to normative database was obtained. The average RNFL reported from different studies in Indian population ranges from 95 μm ± 10 μm in the 18–50-year age group and for this study, 95–115 μm was taken as normal.[13] Average RNFL thickness value of each eye was automatically calculated from the respective mean values and for our study, we considered RNFL thickness <85 μm as thin RNFL.

Brain imaging

All patients underwent MRI imaging of the brain under a standard pituitary scanning protocol, including delayed contrast studies. Optic chiasm compression was recorded using coronal T2W/TSE sequences due to high resolution of the chiasm. Hardy's classification modified by Wilson was used to grade suprasellar extension and sphenoid sinus invasion [Table 1].[14] Fujimoto's criteria were used to grade the severity of optic chiasm compression [Table 1].[15] Chiasmal lift was calculated as described by Frisén and Jensen and defined as the perpendicular distance between the inferior aspect of the chiasm and the sagittal line between the dorsal-most aspect of the olfactory bulbs and the pontomesencephalic junction as measured in the pre-operative T1-weighted scans of all patients [Figure 1].[16]

Table 1: Wilsons modification of Hardy's classification.

Type A	Tumor bulges into the chiasmatic cistern
Type B	Tumor reaches the floor of the third ventricle
Type C	Tumor is more voluminous with extension into the third ventricle up to the foramen of Monro
Type D	Tumor extends into temporal or frontal fossa
Type E	Extradural spread (extension into or out of the cavernous sinus)
Fujimoto grading of severity of optic chiasm	
Grade 0	Tumor has no contact with optic chiasm
Grade 1	Tumor has contact with optic chiasm without the deformity of upper surface of optic chiasm
Grade 2	Tumor compressed optic chiasm and produced the deformity of the upper surface and visible suprachiasmal cistern
Grade 3	Tumor compressing optic chiasm with invisible suprachiasmal cistern
Grade 4	Tumor compressing optic chiasm with cerebral deformity

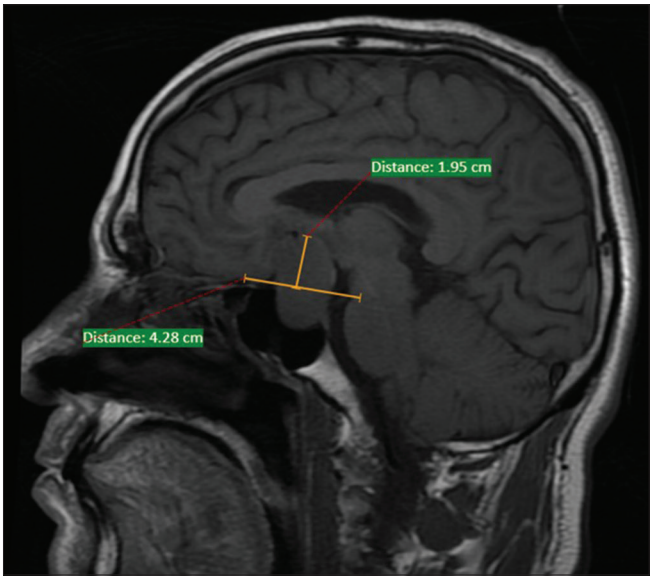

Figure 1: T1-weighted magnetic resonance image (Sagittal midline) of a pituitary macroadenoma demonstrating calculation of chiasmal lift. Chiasmal lift represents the perpendicular distance between the inferior aspect of the chiasm and the sagittal line between the dorsal-most aspect of the olfactory bulbs and the pontomesencephalic junction.

The optic chiasm thickness was measured in the right, left, and center by measuring the vertical diameter on the right side, left side, and the middle part. The distance between the superior margin of the tumor and the inferior surface of the optic chiasm was measured as shown in [Figure 2].

Statistical analysis

IMB SPSS 26.0 software was used for statistical analysis. The association of RNFL thickness, optic chiasm-adenoma distance, optic chiasm thickness, and VA was analyzed using Spearman's correlation and $P < 0.05$ was considered significant.

RESULTS

The study group included 100 eyes of 50 patients operated for sellar suprasellar pituitary macroadenomas. The mean age of the study group was 43.86 ± 13.62 (8–76 years) and both genders were equally (Male: Female 26:24) represented.

Visual examination findings including VA, VF, and fundus findings are summarized in [Table 2]. VA impairment (moderate to severe) was observed in only 30% of the affected eyes while field of vision was either moderately or severely affected in 58% of the affected eyes. Moderate-to-severe disc pallor was recorded in 31% of the affected eyes. Radiological findings including suprasellar extension (Wilson modification of Hardy classification), Fujimotos grading, chiasmal lift, and the optic chiasm thickness are depicted in [Table 3]. Nearly 60% (30/50) of the patients had a Wilsons Grade D or E extrasellar extension of the tumor and 50% (25/50) had severe chiasmal compression as represented by Fujimoto Grade 3 or 4. The average RNFL thickness in our cohort was-106.11 ± 9.5 µm. Average thickness for each quadrant was as follows – Inferior – 134.10 ± 16.16 µm; Superior – 133.44 ± 15.50 µm; Nasal – 84.26 ± 16.43 µm; and Temp – 70.72 ± 14.80 µm.

Mean RNLF for the right eye was 83.86 ± 17.20 µm and the mean chiasmal thickness on the right side was 0.28 ± 0.41 mm.

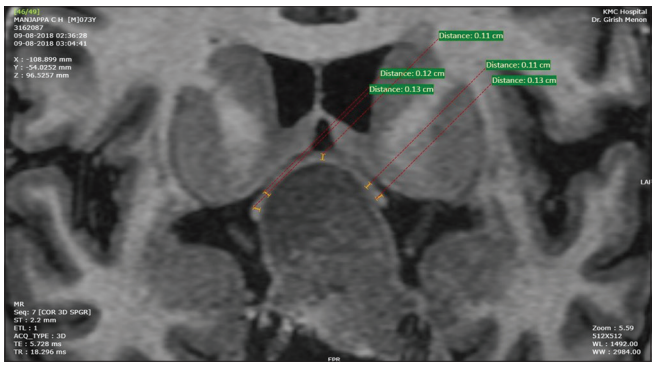

Figure 2: Coronal Flair images of a patient showing measurements of the optic chiasm thickness and the tumor chiasmal distance.

Mean RNFL for the left eye was 86.70 ± 17.21 µm and the mean chiasmal thickness on the left side was 0.25 ± 0.38 mm [Table 3]. The median of the distance between the optic chiasm and PA was 0.18 ± 0.47 (min 0; max 7.6) [Table 3]. Mean chiasmal lift was 1.29 ± 0.87 mm and the thickness of the chiasm at the center was 0.20 ± 0.32 mm.

VA, field, and fundus examinations were dichotomized as Group I (Normal/Mild) and Group 2 (Moderate/Severe). Sub group analysis revealed that mean RNLF values correlated significantly with VA, VF, and fundus. Patients in Group 2 (moderate-to-severe) deficits had proportionately thinner RNFLs compared to patients in Group 1 (normal-to-mild) impairment ($P < 0.05$) [Table 4]. RNFL values were significantly different for various grades of sellar and

Table 2: Visual acuity, visual field, and fundus findings and their correlation with RNFL thickness.

	Number	RNFL thickness	*P*-value
Visual Acuity			
Normal	45	91.93±15.77	<0.001
Mild	25	85.59±12.53	
Moderate	13	82.71±16.02	
Severe	17	69.29±17.18	
Visual Field			
Normal	28	92.45±15.80	0.012
Mild	14	90.32±12	
Moderate	22	82.15±18.27	
Severe	36	79.68±17.18	
Fundus			
Normal	52	93.47±13.64	<0.001
Mild pallor	17	90.23±10.71	
Moderate pallor	22	71.44±12.24	
Severe	09	62.55±15.70	

RNFL: Retinal nerve fiber layer

Table 3: Summary of radiological findings on MRI.

Extrasellar Extension (Wilsons Modification of Hardy grading)	
A	1
B	14
C	5
D	24
E	6
Fujimoto grading	
0	11
1	6
2	8
3	13
4	12
Mean Chiasmal Lift (cm)	1.29±0.87
Mean Chasmal Thickness Right (cm)	0.28±0.41
Mean Chiasmal Thickness - Left (cm)	0.25±0.38
Mean Chiasmal Thickness - Center (cm)	0.20±0.32
Mean Distance between Lesion and Chiasm	0.18±0.47

extrasellar extension, classified by the Wilson-Hardy systems [Table 5]. Wilsons extrasellar extension was dichotomized into two groups, Group A representing Wilson A and B and Group B representing Wilson C, D, and E in another. Mean RNLF values in the Group A was 93.26 ± 13.23 μm and in Group B, it was 81.87 ± 17.61 μm ($P < 0.001$). Fujimoto grading was also split into two groups with Grades 0 and 1 in Group A and Grades 2, 3, and 4 in the Group B. RNLF values in the Group A were 90.85 ± 11.54 μm in comparison to 82.43 ± 18.90 μm ($P = 0.019$) [Table 5]. Chiasmal lift more than 1 cm was associated with thinner RNFLs ($P < 0.002$). Similarly, as the distance between the upper border of the tumor and the chiasm decreased the RNFL became thinner ($P < 0.002$) [Table 5]. RNLF thickness was found to decrease as the chiasmal thickness decreased, but this correlation was not statistically significant ($P = 0.610$) [Table 5].

Table 4: Correlation of visual examination findings with RNFL thickness.

	RNFL	*P*-value
Visual Acuity		
Group 1 (Normal-to-mild)	89.66±14.92	<0.001
Group 2 (Moderate-to-severe)	75.09±18	
Visual Field		
Group 1 (Normal-to-mild)	91.74±14.53	<0.001
Group 2 (Moderate-to-severe)	80.62±17.54	
Fundus		
Group 1 (Normal-to-mild)	92.67±12.98	<0.001
Group 2 (Moderate-to-severe)	68.86±13.69	

RNFL: Retinal nerve fiber layer

DISCUSSION

SD-OCT provides cross-sectional imaging of the retinal layers and helps to analyze the thickness of RNFL and the granular cell layer thickness Ganglion cell complex.[17-19] Pituitary adenomas and other suprasellar tumors produce thinning of the RNFL probably due to their compressive effect on the optic chiasma. Pre-operative RNFL thickness is reported to be an important prognostic factor to predict visual recovery following surgery.[20,21] RNFL assessment thus is an emerging area of research focus in patients with pituitary adenoma, both for quantification of the visual loss and for prognosticating recovery.[22,23]

Thinning of the RNFL generally correlates directly with visual deficits and the extent of chiasmal compression.[17-19] However, this correlation between RNFL thinning, suprasellar extension, chiasmal compression, and visual function is not absolute. Patients with normal-to-mild visual deficits may have RNFL thinning and RNFL may be normal in patients with severe visual deficits.[24,25] Studies have also shown that patients having supra sellar tumors compressing the visual pathway and having normal visual examination may show RNFL thinning.[20,26] Although the loss of RNFL is more severe in patients with chiasmal compression, it has been reported

Table 5: Correlation of RNFL thickness with MRI.

Radiological classification	Mean RNFL thickness		*P*-value
Wilsons modification of Hardy			
Stage A	93.65±0.91	Group A	0.002
Stage B	93.24±13.71	93.26±13.23	
Stage C	89.20±15.41		
Stage D	83.44±17.99	Group B	
Stage E	71.51±14	81.87±17.61	
Fujimoto grading			
Grade 0	96.93±6.90	Group I	<0.001
Grade I	79.70±9.95	90.85±11.54	
Grade II	90.0±04	Group II	
Grade III	84.08±16.31	82.43±18.90	
Grade IV	75.56±17.50		
Chiasmal Lift (cm)			
0–1	91.76±11.70		0.002
1–2	82.43±19.07		
>2	77.23±19.10		
Distance between adenoma and chiasm			
0–0.5	90.07±14.44		0.002
0.5–1	101.33±7.33		
Mean chiasmal thickness			
Mean chiasmal thickness right side (0.28±0.41 mm)	83.86±17.20		0.610
Mean chiasmal thickness left side (0.25±0.38 mm)	86.70±17.21		

RNFL: Retinal nerve fiber layer

that pituitary tumors without optic chiasm compression can also cause thinning of RNFL.[19] This discrepancy is probably because the exact mechanism of RNFL thinning is unknown. RNFL thinning is variably attributed to axoplasmic flow disorder, demyelination,[27-30] ischemic damage,[31-33] changes in metabolites, trophic factors, or proteases associated with an adenoma.[34,35]

Although, the indication for surgery in patients with pituitary macroadenoma is often guided by the quantum of visual deficits, all patients may not have significant visual deficits.[36-40] Anderson *et al*. reported that only 16% of their patients had decreased VA and 32% had VF defects.[1] We made a similar observation and, in our series, VA was affected in only 30% while VF deficits was affected more commonly (58%). The average RNFL thickness in our cohort was 106.11 ± 9.5 μm which surprisingly is higher than the national average.[13] On analyzing the correlation between VA, VF, and optic disc changes in each eye with RNFL changes, we observed a significant relation between RNFL and severity of VA deficit ($P < 0.05$), field deficits ($P < 0.012$), and disc pallor ($P < 0.01$). Patients with moderate-to-severe drop in VA had a RNFL average thickness < 85 μm in our study cohort. Johansson and Lindblom analyzed 16 eyes from eight patients with pituitary adenoma who had bitemporal VF depression but failed to record reduced RNFL thickness in all eyes.[41] Our study contradicts this observation and is similar to the findings reported by Glebauskiene *et al*. and Moon *et al*. who observed that RNFL was significantly thinner in patients with pituitary adenoma compared to the control group.[12,24]

Since the decussating nasal fibers are situated in the center, tumors pressing the optic chiasm compress the decussating nasal fibers preferentially, resulting in retrograde RNFL thinning on the nasal and temporal sides of the optic disc.[42] Reports suggest that thickest RNFL measurements are found in the inferior quadrant, followed by the superior, nasal, and temporal quadrants.[6,12,20,23-26,29,41,43] Our observations were similar with inferior quadrant being the thickest (134.10 ± 16.16 μm) and temporal being the thinnest (56.7 micrometer). As reported by few authors earlier, we found significantly reduced RNFL thickness in the nasal and temporal quadrants in patients with VF defects compared to PA patients with normal VF.[7,20,25,44] RNFL thickness may increase from swelling of the optic disc and may be reduced in optic atrophy[28] and we observed a direct correlation between optic disc head swelling and RNFL thickness with more severe disc pallor corresponding with extremely thin RNFLs (<70 μm).

The correlation between RNFL and MRI measurements of a pituitary adenoma especially in relation to the compression of the optic chiasm has not been extensively studied. Glebauskiene *et al*. in a cohort of 77 patients evaluated RNFL thickness in patients with pituitary adenoma by OCT and compared it with MRI characteristics of pituitary extension in 77 patients.[12] This study perhaps is the second study with a similar objective and is novel in that we have attempted to add two additional features of suprasellar extension – chiasmal lift and Fujimotos grading. Our study observed a significant correlation between Wilsons grade and RNFL thickness ($P < 0.02$), Grades C, D, and E being associated with thin RNFLs. Similarly, patients with Fujimoto Grades 3 and 4 tumors consistently had RNFL thickness <85 μm ($P < 0.05$). Chiasmal lift more than 1 cm was significantly associated with RNFL thickness <82 μm ($P < 0.002$). RNFL thickness were consistently below 90 μm when the distance between the superior surface of adenoma and chiasm is <0.5 mm. The normal reported height of the optic chiasm is around 3.5 mm as described by Parravano *et al*.[45] Reduced chiasmal thickness was associated with thin RNFLs in our study but failed to attain statistical significance as was reported by Glebauskiene *et al*.[12] In patients with suprasellar extension, the chiasmal is often difficult to distinguish and the assessment of its thickness can be erroneous. This probably explains the failure to correlate chiasmal thickness with RNFL thickness.

The clinical benefit of OCT lies in its potential to recognize RNFL thinning even in cases with minimal chiasmal compression which could facilitate speedy treatment of the condition and prevent irreversible visual deficits.[23] The sensitivity of OCT supersedes perimetry testing as RNFL thinning may precede structural loss of axons as detected by OCT. Our study reinforces these observations which firmly define the role of OCT as an important tool in the pre-operative work up of all patients with pituitary adenoma.

Limitations

The major limitation of this study is the limited number. Large studies with OCT analysis are needed to validate these observations. The optic chiasm is often difficult to identify in large tumors with suprasellar extension. Measurement of chiasmal thickness, chiasmal lift can be difficult in such patients.

CONCLUSION

RNFL thickness through OCT provides an objective quantification of visual deficits in patients having pituitary adenoma with suprasellar extension. RNFL thinning correlates directly with the severity of visual deficits. Wilsons Grades D and E, Fujimoto Grades 3 and 4, chiasmal lift more than 1 cm, and chiasm tumor distance <0.5 mm significantly correlate with RNFL thinning. Pituitary macroadenoma needs to be excluded in patients with preserved vision but having obvious RNFL thinning.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study. The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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