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Structural changes in retina (Retinal nerve fiber layer) following mild traumatic brain injury and its association with development of visual field defects

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ABSTRACT

Background: Mild traumatic brain injury (mTBI)is the most common form of traumatic brain injury accounting for 70–80% of all brain injuries annually. There is increasing evidence that long lasting morphological and functional consequence can be present in visual system following mTBI. Among all the visual manifestation, awareness of Visual field defects is important because it may compromise the social, personal or professional life of any individual. Retinal structural changes such as thinning of Retinal nerve fiber layer (RFNL)captured using optical coherence tomography have emerged as a possible biomarker in many neurological diseases however very little is known in cases with mTBI

Objective: (I) To demonstrate the structural changes/morphological changes in retina if any following mTBI. (II) Whether the structural changes in retina have any association with the development of Visual field deficits leading to Visual function impairment following mTBI (III) Clinical relevance of structural changes in retina as a possible biomarker for visual function impairment due to visual field deficits.

Materials and Methods: Our study included 60 patients with mTBI who fulfilled the inclusion criteria. All patients underwent a detailed ophthalmic evaluation with special focus on temporal recording of Retinal nerve layer thickness using SD- Optical Coherence Tomography and Visual field (Visual field Index) by Humphrey Automated Field Analyser.

Results: 30% of eyes had significant thinning of RFNL (> 30% of the base line thickness) at 6 months following mTBI. Visual function impairment due to visual field deficits (VFI < 80%) at 6 months was seen in 40% of the eyes. The structural changes and visual function impairment peaked at 6 months' post injury. A strong Association was noted between RFNL thinning and manifestation of Visual field deficits (VFI < 80%) leading to visual function impairment ($P < 0.001$). The Correlation Co-efficient between thinning of RFNL and Visual field deficits had a positive correlation($p < 0.001$).

Conclusion: This novel study has demonstrated that visual functional impairment due to Visual field deficits is a real possibility following mTBI. Monitoring of retinal parameter such as thinning of Retinal nerve fiber layer, using Optical coherence tomography, can be a biomarker for early detection or development of visual field defects in mTBI.

1. Introduction

Traumatic brain injury poses a major public health problem worldwide [1]. It imposes a tremendous burden on health care systems through disability and cost of care. The majority of traumatic brain injuries that occur each year are concussions or other forms of mTBI (70%–80%) [2]. Patients with mild traumatic brain injury (mTBI) would rarely come to neuropathological examination but there is increasing evidence that some permanent brain damage is also present.

Mild Traumatic brain injury can manifest in a number of different

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ways, but one of the most significant and often debilitating one is its impact on the visual system. It is not surprising that a constellation of visual dysfunction and related symptoms arise due to traumatic brain injury since there are more than 30 brain areas associated with visual functioning as well as seven of the twelve cranial nerves [3].

There also appears a strong possibility of developing retinal tissue changes following mild traumatic brain injury since traumatic brain injuries can lead to secondary brain insults due to a wave of excitotoxic, metabolic and inflammatory cascades in addition to primary impact of coup, contra-coup acceleration /deceleration forces to brain [4,5]. The effect may be more pronounced in retina because it is one of the most metabolically active tissue of the body [6].

Identification of visual deficits or problems following mTBI is challenging. For one, the diagnosis is often delayed because symptoms develop over a period of time. By the time patients visit the doctor, they are usually frustrated and worried. They are anxious to get back to their normal personal & professional life. Among many visual manifestations, awareness of Visual field loss is important because it may endanger the life of the patients and others. In this backdrop the need was felt for identifying some biomarker which might help in predicting the possibility of patients suffering from visual field defects following mTBI.

There is emerging evidence where in the structural changes in retina in the form of thinning of Retinal nerve fiber layer (RFNL) captured using Optical coherence tomography is showing some promise as a biomarker for many neurological disorders such as multiple sclerosis, neuromyelitis Optica, Parkinson's disease and Alzheimer's disease [7,8]. However very few reports are available or far less is understood about how mild traumatic brain injury would affect the retinal thickness.

Therefore, the focus of our study was.

I. To determine the structural changes/morphological changes in retina following mTBI.
II. Whether the structural changes in retina following mTBI have any association with the development of Visual field defects leading to Visual function impairment.
III. Clinical relevance of structural changes in retina following mTBI as a possible biomarker for visual function impairment due to visual field deficits.

2. Methods and material

This is a prospective observational study conducted in the Departments of Neurosurgery and Ophthalmology of a tertiary health care hospital in Eastern India.

2.1. Inclusion criteria

All the patients, above the age of 18 years, diagnosed clinically as mild traumatic brain injury were recruited for the study.

2.2. Exclusion criteria

Patients with eye disorders such as Glaucoma, Advanced Cataract, Retinal diseases, Corneal and lens opacities, past history of intraocular surgery, Psychiatric illness were not included in the study. Any patient with visual acuity less than 20/40 was excluded from the study.

2.3. Study duration

This study was conducted between July 2017 to July 2020. Each patient was followed up and assessed at 7 days, 3 months, 6 months and 1-year post trauma.

3. Methodology

A detailed ophthalmic workup which included Optical coherence tomography for RNFL thickness using the Cirrus HD-OCT (500-22681, Carl Zeiss Meditec Inc.) and Visual field testing using the Humphrey Automated Field Analyzer (Carl Zeiss Meditec, Inc. Dublin, California, USA, Model 745i) was done for every patient.

3.1. Mild traumatic brain injury

WHO Operational criteria for clinical identification of mTBI was taken for our study. The criteria include (a) State of confusion, disorientation and loss of consciousness not exceeding 30 min (b) Post traumatic amnesia for as much as 24 h (c) A Glasgow coma scale of 13–15 after 30 min' post injury or at presentation to the hospital.

3.2. Neuroimaging

CT scan of Brain and Orbit (Non-Contrast) was done at first visit and at one-month post injury.

3.3. Visual functional impairment

Visual functional impairment due to visual field deficit may manifest in the form of difficulty in driving, blurring of vision while watching TV, difficulty in reading and tendency to run into things. The presence of any one of these symptoms was considered to be visual function impairment.

3.4. Visual field testing

Field testing was done using the program 30–2 SITA (Swedish interactive threshold algorithm) standard. Each eye was tested separately, and all eyes were tested by the same operator. Test results with poor reliability were excluded from the study. Reliability criteria was defined as less than 20% fixation loss and less than 33% for both false positive and false negative errors [9].

3.5. Visual field index

VFI, which is a global index incorporated in the software of the Humphrey Field Analyzer, was used to determine the extent of visual field damage. A VFI index of 100% was taken as normal visual field while VFI of 0% was considered as perimetrically blind field [10,11]. We have taken a VFI of 80% or less as a significant visual field deficit for our study. Visual field index at seven days' post injury was taken as the baseline measurement for that particular eye.

VFI has become an accepted standard for describing the overall status of visual fields in individuals as well as in groups enrolled in research studies [12].

3.6. Optical coherence tomography

OCT-RNFL (Retinal Nerve Fiber Layer) was measured with Cirrus OCT Spectral domain technology using CIRRUS HD-OCT (500-22681) Carl Zeiss Meditec Inc. Scans with signal strength of 5/10 or more were taken. All scans were done by the same operator. In this study peripapillary retinal nerve fiber layer thickness was assessed. Three circular scans with 3 mm diameter centering ONH (optic nerve head) were used for calculating average RNFL thickness in microns (πm).

3.7. Retinal nerve fiber layer

The 7th day post mTBI measurement of average RNFL was taken as the baseline control measurement for that particular individual. The 7th day average RNFL thickness was compared with average RNFL thickness at 3 months and 6 months and one year respectively for the same

individual.

A reduction of 30% or more in RFNL thickness as compared to baseline control measurement of that individual was taken as significant loss of thickness.

4. Statistical analysis

Graphed Prism 9 software was used to analyse the variables. Statistical significance (P value ≤ 0.01) was determined by using Fisher Exact Test.

The analysis to understand whether a correlation existed between RFNL thinning and Visual field defects was done using Pearson's correlation test. Statistically significance was taken at $P < 0.01$.

4.1. Data management

Consent was taken from patients before enrolling them in the study.

Assessment and documentation were supervised by the same individual.

Study Commenced after the approval from Institutional Ethics committee.

5. Results

A total of 60 patients with Mild traumatic brain injury consented and were found suitable to be included in this study. 106 eyes were assessed for this study. 6 patients were lost to follow up. Two patients were one eyed.

There were 36 male patients and 24 were females in our study group. 63.4% of patients were less than 45 years in age while 36.6% were more than 45 years in age. Visual Acuity at time of recruitment for the study was 20/20 among 79.3% patients while 20.7% patients had visual acuity of 20/40. Clinically no patient had any evidence suggestive of trauma involving optic pathways [Table 7].

5.1. Neuroimaging

The CT scan of brain and orbit was normal for 54 patients. 6 patients had tiny contusion involving the frontal and cerebellar region however none of the patients had any lesion involving the optic pathway.

5.2. RFNL thinning

At 3 months' post mTBI, 31% of patients showed reduction (> 20%) in thickness of RNFL, while 22% patients had more than 30% reduction in thickness. RNFL measurement at 6 months showed further thinning. At 6 months 30% of the patients had more than 30% reduction in RFNL thickness compared to their baseline measurements. However, at 12 months the percentage of eyes with > 30% RFNL thinning remained similar to the levels seen at 6 months (Table 1).

Mean RFNL thickness at different time intervals is presented (Table 2) which shows that RFNL thinning peaked at around 6 months. In some cases, the RFNL thinning continued up to one year.

Table 1
OCT measurements for RNFL thickness at 3 month, 6 months @ 12 months post injury. (RFNL thickness at 7 days post injury is taken as base line.).

	Average RFNL Measurement	@ 3 months post injury	@ 6 months post injury	@ 12 months post injury
1	No change in thickness	46 (43.3%)	40 (37.7%)	42 (39.6%)
2	Increased Thickness	04 (3.7%)	0 (0%)	0
3	20% reduction in thickness	33 (31%)	35 (33%)	35 (33%)
4	30% reduction in thickness	23 (22%)	31 (29.3%)	29 (27.4%)

Table 2
RFNL thickness (Mean with SD) at different time periods post injury.

RFNL thickness.							
@ 7 days		@ 3 months		@ 6 months		@ 12 months	
Mean	SD	Mean	SD	Mean	SD	Mean	SD
104.1	4.61	90.1	13.3	86.8	13.0	86.1	12.6

5.3. Visual field defects (visual field index)

44% of the eyes had VFI of less than 80% at 3 months' post mTBI. At 6 months the VFI (< 80%) was noted in 40% of the eyes which remained at similar levels at one year (Table 3). The peak period for developing visual field defects (VFI < 80%) was at three months' post injury. Visual field loss appeared to be stabilizing at 6 months and remained almost the same at 12 months. The most frequent Visual field defect documented in our study was scatter field defect (Table 4).

5.4. Visual functional impairment and visual field loss/defects

Among the study population, 43.3% of eyes had visual symptoms due to visual field loss at 3 months' post injury; however by 6 months & one year approximately 47% of patients complained of visual symptoms related to visual field defects.

On analysing the association of Visual functional impairment due to Visual field loss as documented by Visual field index, we found that visual function impairment was more pronounced in eyes which recorded VFI < 80%. ($P < 0.001$) (Table 3).

5.5. Association between age and gender with RFNL thinning following mTBI

The effect of age or gender on RFNL thinning following mild traumatic brain injury was found to be statistically not significant (Table 7).

5.6. Association between RFNL thinning and visual field index

The association between the extent of RNFL thinning and VFI suggest that whenever there is more than 30% decrease in RNFL thickness from the baseline control thickness at 7 days' post mTBI, the possibility of developing visual field defects (VFI< 80%) becomes statistically significant. ($P < 0.001$). This association remained valid at 3 months, 6 months and one-year post injury (Table 5).

5.7. Correlation coefficient between RFNL thinning and VFI

Correlation Coefficient and its P value between RFNL thickness change and VFI following mTBI showed a positive correlation between the thinning of RNFL (30% or more) and visual field defect (VFI <80%) leading to visual function impairment (Table 6).

5.8. Summary of results

- 30% of eyes had significant thinning of RFNL (>30% of the baseline control thickness) at 6 months following mTBI.
- 40% of the eyes showed significant visual function impairment due to visual field defects (VFI < 80%) at 6 months following mTBI.
- Scatter Visual field defects were the most frequently documented field defects in our study.
- The structural changes and visual function impairment peaked at 6 months following injury.
- A strong Association was noted between RFNL thinning and manifestation of Visual field defects (VFI < 80%) leading to visual function impairment. The association was statistically significant ($P < 0.001$) when RFNL thinning was > 30% of the baseline control.

Table 3
Visual field index changes at 3 month, 6 months and 12 months post injury. (Visual field index at 7 days post injury is taken as base line.).

		@ 3 months post injury		@ 6months post injury		@ 12 months post injury	
		Asymptomatic	Symptomatic	Asymptomatic	Symptomatic	Asymptomatic	Symptomatic
1	VFI (80–100%)	51(48.2%)	8(7.5%)	53(50%)	10(9.4%)	54 (51%)	10(9.4%)
2	VFI (<80%)	9(8.5%)	38(35.8%) **(p < 0.001)**	3(2.8%)	40(37.8%) **(p < 0.001)**	2 (1.8%)	40(37.8%) **(p < 0.001)**

Table 4
Types of Visual field defects following mTBI.

		@ 3 months	@ 6 months	@ 12 months
1	**none**	59 (55.6%)	63 (59.5%)	64 (60.4%)
2	**Scatter**	29 (27.4%)	28 (26.3%)	28 (26.3%)
3	**Hemianopia**	3 (2.8%)	2 (1.9%)	2 (1.9%)
4	**Quadrantanopia**	2 (1.9%)	1 (0.9%)	
5	**Altitudinal**	4 (3.7%)	3 (2.8%)	3 (2.8%)
6	**Central**	2 (1.9%)	2 (1.9%)	2 (1.9%)
7	**Constricted**	7 (6.7%)	7 (6.7%)	7 (6.7%)

- The Correlation Co-efficient between thinning of RFNL and Visual field defects had a positive correlation with a p value ($p < 0.001$).

6. Discussion

Structural changes in retina in the form of alteration in thickness of RNFL (Retinal nerve fiber layer) following concussion or mild traumatic brain injury or traumatic optic neuropathy have been reported [17,30] however none of the studies have captured any association between retinal changes and visual functional impairment following mTBI. Few animal model studies on mTBI have documented visual functional impairment and retinal changes in form of retinal nerve fiber layer thinning [18,19].

In our study we have taken RFNL layer to monitor the structural changes in retina following mTBI because the retinal nerve fiber layer (RNFL) constitutes axonal fibers of retinal ganglion cells (RGC) forming optic nerve. RNFL captures visual information for the brain and appears sensitive to pathological brain changes [31]. Retrograde degeneration of retinal ganglion cell axon may be the possible reason for retinal changes following mTBI [16].

Optical Coherence tomography (OCT) was our means to monitor and document the changes in RFNL. It has emerged as a promising tool for detecting and quantifying structural axonal damage in neuroscience research because of its proven high reliability in various CNS pathologies and good correlation with many visual electrophysiological techniques [20,21,25,26]. The structural changes in retina in the form of thinning of Retinal nerve fiber layer captured using optical coherence tomography (OCT) has shown some promise as a biomarker for many neurological disorders [7,8,13–15] but not much is known in cases with mTBI.

Monitoring the structural changes in retina and documenting its temporal progress using Optical coherence tomography (OCT) was done at 7 days, 3 months, 6 months and 12 months following mTBI. The timeline of monitoring was based on few studies that have suggested that hardly any structural changes are noticed in retina earlier than 7 days' post injury, thinning may start around two weeks post trauma and may continue up to 20 weeks to 6 months [17,18,22,23].

Seven days' post injury measurement of RFNL thickness was taken as our baseline control measurement because standardized RFNL thickness measurements are not available. Thickness measures vary among normal individuals as well as they vary with age, gender and race [24].

Since there is very limited literature available on the extent of retinal thinning to be considered abnormal, we decided to consider more than 30% reproducible reduction in average RNFL thickness when comparing two observations from the same eye on two different visits as compared to the control baseline measurement as abnormal. An association between 30% reduction in RFNL thickness with abnormalities in automated perimetry in traumatic optic neuropathy has been reported [30]. However this association has not been examined in cases with mTBI.

Visual field index (VFI) was taken as the measure for documenting and monitoring visual field deficit in our study because it estimates the rate of change in visual fields and reflects the amount of overall Visual field deficits as percentage. [32].

Retinal nerve fiber layer (RFNL) thinning was evident by the third month post injury. At three months, 22% of patients had more than 30% reduction in thickness as compared to the baseline control measurement of 7 days. The peak period when the RFNL thinning was documented was at 6 months' post injury. The structural changes in retina stabilized at 6 months. At one year, the percentage of eyes with RFNL thinning remained almost at the same levels as observed during 6 months' post injury (Table 1). Our study reconfirms the observations reported from few a animal studies suggesting a strong probability of developing retinal structural changes following mTBI in human beings also.

Although Visual Field deficits are seen in severe forms of traumatic brain injury, few reports have suggested that Visual Field deficits are also common in patients who have sustained mTBI. The frequency of Visual field defects was in the range of 35–41% in various reports. Goodrich in his report indicated that 24% of those with brain injuries had some sort of VF defects [27], whereas Sabates et al. found that 35% of head trauma patients had VF defects with tunnel vision (i.e., constricted) being most prevalent (41%) [28]. In our series scatter field defects were more commonly encountered.

In a study by Maj David V. Walsh, the report indicated that the Visual Field defects are common, i.e., up to 60% in patients with mTBI however a decreasing trend in these defects was seen over time. They also noted a significantly high frequency of scatter visual field defects (48%) [29].

On analysing our data, we found that 47% of the eyes studied had Visual field defects (VFD)following mTBI. The peak period for

Table 5
Association between RFNL thickness & Visual field loss (VFI).

		@ 3 months post injury		@ 6 months post injury		@ 12 months post injury	
	RNFL thickness	VFI (< 80%)	VFI (80–100%)	VFI (< 80%)	VFI (80–100%)	VFI (< 80%)	VFI (80–100%)
1	No change	10 (9.3%)	36 (34%)	6 (5.6%)	34 (32.1%)	6 (5.6%)	34 (32.1%)
2	Increased Thickness	0	4 (3.7%)	0	0	0	0
3	> 20% reduction in thickness	14(13%)	19(18%)	10 (9.3%)	25 (23.6%)	12 (11.4%)	25 (23.6%)
4	> 30% reduction in thickness	23 (22%) **(p < 0.001)**	0	27 (25.7%) **(p < 0.001)**	4 (3.7%)	25 (23.6%) **(p < 0.001)**	4 (3.7%)

Table 6
Association Co efficient and P –Value between RNFL thickness changes & Visual field Index.

Association Co efficient and P –Value					
@ 3 months		@ 6 months		@ 12 months	
Coefficient	P Value	Coefficient	P Value	Coefficient	P Value
0.54	< 0.0001	0.48	< 0.0001	0.40	< 0.001

Table 7
Association of RFNL thickness with age, gender, Visual acuity, optic pathways involvement (Afferent pupillary defects & Neuroimaging).

RFNL thinning@ 1 year	AGE (n = 60 patients)		Gender (n = 60 patients)		Visual Acuity@ 7days post injury (n = 106 eyes)		CT scan (Brain) (n = 60 patients)	RAPD[a] (n = 106 eyes)
	< 45 years	> 45 years	male	female	20/20	20/40	Optic pathway involvement	
RFNL thinning > 30%	20(33.4%)	11(18.3%)	19(31.7%)	12(20%)	46(43.4%)	12(11.3%)	nil	nil
RFNL thinning < 30%	18(30%)	11(18.3%)	17(28.3%)	12(20%)	38(35.9%)	10(9.4%)	nil	nil

[a] RAPD: Relative Afferent pupillary defect.

developing visual field defects was three months. Our data also indicates that in a few patients who had Visual field deficits at 3 months improved by 6 months. At one year, the percentage of patients with Visual field defects remained at the same levels as seen at six months' post injury. Our findings regarding visual field deficits following mTBI are similar to what is reported in various studies.

This study has also demonstrated that in patients with mTBI, when there were Visual field defects amounting to VFI of 80% or less, there were profound visual symptoms or impairment. The association between VFI (80% or less) with visual functional impairment was statistically significant following (Table 3). This association has not been reported earlier.

When we looked into the association between structural changes in retina in the form of RFNL thinning and visual field defects, we observed that when the RFNL thinning was more than 30% from its baseline control recording, there was a strong probability of encountering visual field deficits(VFI < 80%). This was statistically significant (Table 5).

Correlation Coefficient and P value between retinal structural change and VFI showed significant positive correlation between the thinning of RNFL (30% or more) and visual field defect (VFI < 80%) leading to visual function impairment.

This study has very clearly demonstrated that the development of visual functional impairment due to visual field defects following mTBI is a real possibility and should be looked up for at least up to 6 months following trauma. A very strong association has emerged between visual functional impairment due to visual field deficits and the structural changes in retina in the form of thinning of Retinal nerve fiber layer following mTBI thus opening up the possibility of serial monitoring RFNL layer thickness using OCT as predictor or biomarker for development of visual field deficits following mTBI.

6.1. Limitations

This was a single center study and may be the only study where association between structural changes in retina leading visual functional impairment due to Visual field defects following mTBI has been documented. Similar studies would be required for reconfirmation of the observations and findings generated in this study.

7. Conclusions

This study has indicated that structural changes in retina leading to thinning of retinal nerve fiber layer following mTBI is a real possibility. OCT imaging has emerged as a very useful tool for documenting and monitoring the progress of structural changes in retina following mTBI. Capturing of RFNL thinning following mTBI can be a strong biomarker and predictor for the development of visual field deficits leading to visual functional impairment.

Ethics approval and consent to participate

Study was commenced after receiving approval from Institutional Ethics committee.

CRediT authorship contribution statement

Narendra Kumar Das: Concept, Literature search, clinical study, Data acquisition, Statistical analysis, manuscript review. **Matuli Das:** Literature search, Clinical study, Data analysis, Manuscript preparation.

Disclosures

The authors have no conflict of interest to report.

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