

Afferent visual manifestations of traumatic brain injury

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Table 1: Classification of TBI severity

Criteria	Mild	Moderate	Severe
GCS score	13-15	9-12	less than or equal to 8
Post-traumatic amnesia	Up to 24 hours	24 hours to 1 week	More than 1 week
Loss of consciousness	Up to 30 minutes	30 minutes to 24 hours	More than 24 hours
Alteration of consciousness/mental state	Up to 24 hours	More than 24 hours, severity based on other criteria	More than 24 hours, severity based on other criteria

Table 2: Summary of pupillometry parameters data between normal controls and mild TBI patients

Pupil parameters	Capo-Aponte et al. ⁷⁹		Thiagarajan & Ciuffreda ⁸⁰		Truong et al. ⁸¹		Truong et al. ⁸³			
	Control	Mild TBI	Control	Mild TBI	Control	Mild TBI	Control with photosensitivity	Control without photosensitivity	Mild TBI with photosensitivity	Mild TBI without photosensitivity
Max. pupil diameter (mm)	5.63	5.50	5.8	5.2	6.66*	6.02*	6.64	6.49	5.99*	5.64*
Min. pupil diameter (mm)	3.78	3.62	3.8	3.6	4.57*	4.01*	3.68	3.85	3.47*	3.16*
Constriction latency (s)	0.211**	0.239**	0.209	0.219	0.199*	0.214*	0.198	0.190	0.201	0.207
Average constriction velocity (mm/s)	4.11*	3.58*	4.4**	3.6**	2.55	2.39	2.62*	2.36*	2.23	2.16
Peak constriction velocity (mm/s)	5.15	4.91	5.8**	4.8**	5.75	5.47	6.59*	5.95*	5.75	5.78
Average dilation velocity (mm/s)	1.02*	0.80*	1.1**	0.9**	0.79	0.75	0.86	0.83	0.78	0.76
Amplitude constriction	N/A	N/A	2.1**	1.6**	2.09	2.01	3.01*	2.64*	2.52	2.49
Peak dilation velocity (mm/s)	N/A	N/A	N/A	N/A	1.83*	1.64*	1.89	1.92	1.72*	1.59*
6 sec post-stimulus diameter (mm)	N/A	N/A	N/A	N/A	6.49*	5.76*	5.68	5.79	5.21	4.84
75% recovery time (sec)	1.77**	4.47**	2.4	2.2	N/A	N/A	3.50	3.27	3.16*	3.65*

* Indicates p<0.05; ** indicates p<0.0001

Table 3: Studies of retinal changes in TON patients using SLP

Study	Sample size	Metrics	Findings
⁹⁸ Medeiros et al. (2001)	n=1	RNFL	Progressive RNFL thinning after 15, 30, 45 and 90 days of injury
⁹³ Meier et al. (2002)	n=5	RNFL	RNFL thinning within 7-8 weeks post-injury; 2 patients showed initial RNFL thickening during the first 14 days after injury
¹⁰⁰ Miyahara et al. (2003)	n=1	RNFL	RNFL thickening (all quadrants except superior) at day 1, 9 and 16 post-injury, and progressively decreased in all quadrants after 16, 25, 53, 90 and 120 days of injury.
⁹⁹ Kuo et al. (2005)	n=1	RNFL	No changes observed within the first 14 days but deviation (mix of thickening and thinning at different quadrants) started at day 63 until day 91 post-injury.

RNFL= retinal nerve fiber layer; SLP= scanning laser polarimetry

Table 4: Studies of retinal and visual changes in TON and TBI patients

Study	Study design and sample size	Inclusion Criteria	Type of OCT	Metrics	Findings	Other visual changes
⁷⁵ Medeiros et al. (2003)	Prospective observational n=1	TON	TD	RNFL	Global RNFL thickness decreased from 135µm at day-3 to 81µm, 63µm, and 21µm at 20, 40, and 70 days after injury.	Initial VA NLP in the right eye and 6/6 in the left eye. progressing at day-70 to NLP in both eyes.
⁷⁶ Vessani et al. (2007)	Prospective observational n=1	TON	TD	RNFL and macular	Progressive macula thinning from 183µm at day 7, to 169µm, 172µm and 167µm at 28, 49 and 77 days after injury. Similar trend was noted for RNFL however no actual value reported.	Initial VA hand motion in the right eye and 6/6 in the left eye.
¹¹⁰ Cunha et al. (2009)	Prospective observational n=3	TON	TD	RNFL and macular	RNFL and macular thickness reduced sequentially from day-7 (114µm and 248µm) until day-84 (46µm and 218µm).	Two subjects had initial VA of light perception improving to hand movement at day-84. One subject initial hand movement improved to 6/120 at day-84.
¹⁰⁹ Kanamori et al. (2012)	Prospective observational n=4	TON	SD	RNFL, GCC	Both RNFL & GCC stable at day-7 but began thinning at day-14 onwards. Total macula thinning by day-28.	Three subjects presented with NLP in the affected eye and one improved to 6/120 at day-140. Subject 4 presented with 4/60 and improved to 6/6.

and
macular

¹¹⁶ Kardon et al. (2013)	Cross-sectional observational n=54	Veterans with mild TBI	SD	RNFL and GCC	Average RNFL thinning to below 5 th percentile in TBI patients was 14.8% and 7.6% more frequent in right eyes and left eyes, in controls and GCC 24.5% and 14.8% more frequent in right and left eyes.	Not reported.
¹¹¹ Shi et al. (2013)	Prospective observational n=54	TON	SD	RNFL	RNFL began thinning at day-28 in NLP and day-14 in better than NLP.	Initial VA for better than NLP group was 3.9 EDTRS letters (between light perception to 6/60). No final VA reported.
⁴³ Bixenmann et al. (2014)	Cross-sectional observational n=107	Football players with TBI vs without	SD	RNFL and GCC	Significant RNFL thickening in concussion (107μm) compared to non-concussion group (104μm). Similar GCC (98μm vs 97μm, p=0.15)	Not reported.
⁸⁶ Lee et al. (2016)	Cross-sectional observational n=29	TON	SD	RNFL, GCC and retina	No difference between affected and unaffected eyes for all RNFL sectors, entire retina and inner GCC, except outer nasal (90μm vs 95μm), outer superior	Mean VA of the affected and unaffected eyes was 6/36 and 6/6, respectively. The visual field mean deviation was -17.6±12.6 dB for affected eyes; and -1.9±1.4 dB for unaffected eyes. Mean color vision

(80µm vs 88µm) and outer inferior (81µm vs 90µm) GCC. (Ishihara 15-plate) was 3.6/15 and 14.9/15 for affected and unaffected eyes.

¹¹² Childs et al. (2018)	Prospective observational n=16	Olympic boxers with mild TBI	SD	RNFL and macular	Macular thickness increased between baseline and 18 months in right eye (271µm vs 276µm) and left eyes (268µm vs 276µm). Also, superior (115µm vs 120µm) and inferior (124µm vs 127µm) RNFL right eye, and inferior (127µm vs 132µm) RNFL left eye.	Not reported.
⁴² Leong et al. (2018)	Cross-sectional observational n=46	Sports- related TBI	SD	RNFL and GCC	Average RNFL thickness for boxers reduced compared to controls (84µm vs 94µm). No difference between football and hockey players and controls. Average GCC lower in boxers than controls (77µm vs 82µm). No difference noted between football and hockey players and controls.	Average VA measured 55.8 (~6/24), 59.7 (~6/19) and 60.4 (~6/19) EDTRS letters for boxers, American football players and controls.

⁷⁷ Lee et al. (2019)	Prospective observational n=2	TON	SS	RNFL and GCC	<p>Case 1, RNFL thickness decreased from 129µm at day-1 to 124µm, 114µm, 97µm and 54µm at 2, 7, 30 and 120 days after injury. GCC static at day-2 compared to day1 (109µm vs 108µm), and reduced to 107µm, 80µm and 67 at day 7, 30 and 120 days.</p> <p>Case 2: Gradual RNFL thinning from 107µm to 98µm, 86µm, 45µm and 35µm from day-1 to day-7, 14, 60, 150 post injury. GCC gradual thinning (110µm, 107µm, 94µm, 64µm and 59µm).</p>	<p>Initial VA counting fingers and hand movements.</p> <p>Visual field defects improved over time.</p>
⁸⁸ Chan et al. (2019)	Retrospective observational n=19	Veterans with mild TBI vs healthy controls	SD	RNFL and GCL	<p>Temporal RNFL was significantly thinner in mild TBI patients (61.5µm) compared to controls (75µm). No difference in GCL.</p>	<p>Mean logMAR VA 0.068±0.120 (~6/7.5±6/7.5) right eye and -0.042±0.121 (~6/6±6/7.5) left eye. No RAPD in any subject. Visual field mean deviation -4.67±6.61 dB right eye and -4.05±5.55 dB left eye including superior or inferior arcuate defects and paracentral scotomas.</p>
⁸⁷ Singh et al. (2019)	Prospective observational	TON	SD	RNFL	<p>At baseline (day-7-28), right eye RNFL thickness lower than controls in nasal</p>	<p>Initial VA was 6/12 and 6/9.5 for the right and left eyes respectively. No improvement noted after 3</p>

n=108

(59 μ m vs 68 μ m), inferior (110 μ m vs 124 μ m) and temporal (70 μ m vs 78 μ m) quadrants and superior (117 μ m vs 122 μ m), nasal (66 μ m vs 76 μ m) and temporal (60 μ m vs 64 μ m) quadrants in the left eye.

Contrast sensitivity (Pelli-Robson) improved from 1.2 log unit at presentation to 1.07 log at 3 months for both eyes.

After 3 months, superior RNFL showed progressive thinning compared to baseline in right (123 μ m vs 115 μ m) and left eyes (117 μ m vs 111 μ m).

⁴¹ Kelman et al (2020)	Cross-sectional observational n=13	Sport-related mild TBI	SD	RNFL	All TBI subjects had thinned RNFL in most sectors (average 4 μ m) compared to matched Heildelberg normative data especially left nasal (10 μ m thin) and left inferonasal (14 μ m thin).	Mean VA right eye 6/9.5 and left eye 6/6. Three superior field defects and one inferior arcuate defect.
¹¹⁷ Gilmore et al (2020)	Prospective observational study n=139	Veterans with mild TBI vs veterans without TBI	SD	RNFL and GCC	Veterans with mild TBI had more RNFL thinning over time (1.47 μ m/year) compared to veterans with no TBI history (0.31 μ m/year) (p=0.001). No difference in	No difference in visual acuity between groups. Visual field mean deviation and pattern standard deviation declined more over time in TBI than to controls (-0.09dB/year vs 0.46dB/year;

GCC thickness (mild TBI: 0.17 μ m/year; 0.09dB/year vs -0.10dB/year). Contrast sensitivity
controls: 0.02 μ m/year, p=0.51) worse (12 cycles/degree) in TBI than controls.

OCT= optical coherence tomography; TBI= traumatic brain injury; TON= traumatic optic neuropathy; RNFL= retinal nerve fiber layer; GCC= ganglion cell complex;

GCL= ganglion cell layer; TD= time domain; SD= spectral domain; SS= swept source; EDTRS= Early treatment diabetic retinopathy study