Afferent visual manifestations of traumatic brain injury

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DOI:
10.1089/neu.2021.0182

Document Version
Peer reviewed version

Citation for published version (Harvard):
Saliman, NH, Belli, A & Blanch, R 2021, 'Afferent visual manifestations of traumatic brain injury', *Journal of Neurotrauma*, vol. 38, no. 20, pp. 2778-2789. https://doi.org/10.1089/neu.2021.0182

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 5th 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	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. 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).	Initial VA counting fingers and hand movements. Visual field defects improved over time.
[88]Chan et al. (2019)	Retrospective observational n=19	Veterans with mild TBI vs healthy controls	SD	RNFL and GCL	Temporal RNFL was significantly thinner in mild TBI patients (61.5μm) compared to controls (75μm). No difference in GCL.	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.
[87]Singh et al. (2019)	Prospective observational	TON	SD	RNFL	At baseline (day-7-28), right eye RNFL thickness lower than controls in nasal	Initial VA was 6/12 and 6/9.5 for the right and left eyes respectively. No improvement noted after 3

	n=108				(59µm vs 68µm), inferior (110µm vs 124µm) and temporal (70µm vs 78µm) quadrants and superior (117µm vs 122µm), nasal (66µm vs 76µm) and temporal (60µm vs 64µm) quadrants in the left eye. After 3 months, superior RNFL showed progressive thinning compared to baseline in right (123µm vs 115µm) and left eyes (117µm vs 111µm).	months. Contrast sensitivity (Pelli-Robson) improved from 1.2 log unit at presentation to 1.07 log at 3 months for both eyes.
[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 4µm) compared to matched Heildelberg normative data especially left nasal (10µm thin) and left inferonasal (14µm 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 (1.47µm/year) compared to veterans with no TBI history (0.31µm/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: 0.17μm/year; controls: 0.02μm/year, p=0.51)	0.09dB/year vs -0.10dB/year). Contrast sensitivity 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