Indirect Traumatic Optic Neuropathy in Mild Chronic Traumatic Brain Injury

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Submitted: October 30, 2018
Accepted: April 8, 2019

Citation: Chan JW, Hills NK, Bakall B, Fernandez B. Indirect traumatic optic neuropathy in mild chronic traumatic brain injury. *Invest Ophthalmol Vis Sci*. 2019;60:2005–2011. https://doi.org/10.1167/iovs.18-26094

Purpose. To analyze the clinical presentation and optical coherence tomography (OCT) findings in indirect traumatic optic neuropathy (ITON) in veterans with chronic mild traumatic brain injury (mTBI).

Methods. This retrospective study is the first to describe the OCT pattern of subclinical to mild ITON in veterans with chronic mTBI. The thicknesses of the macular ganglion cell layer (mGCL), peripapillary retinal nerve fiber layer (pRNFL), and subfoveal choroidal layer were analyzed in young veterans who had mTBI of >6 months' duration and either blunt head injury or improvised explosive device (IED) concussions.

Results. Three major OCT findings were demonstrated: (1) temporal pRNFL thinning was associated with subclinical TON in the eyes of chronic mTBI patients compared with controls; within mTBI subjects, nasal mGCL thinning at the 3-mm modified Early Treatment Diabetic Retinopathy Study circle diameter distance from the fovea correlated with the corresponding temporal retinal nerve fiber layer thinning; (2) inner (1 mm) superior thinning was greater than that of the temporal mGCL in blunt head injury and could potentially distinguish it from IED concussive head trauma; and (3) subfoveal choroidal thinning was significantly worse in eyes of mTBI patients compared with those of controls.

Conclusions. These OCT findings may contribute to the understanding of the spectrum of visual injuries resulting from head trauma.

Keywords: indirect traumatic optic neuropathy, traumatic brain injury, optical coherence tomography

Most of our knowledge regarding the pathophysiology of indirect traumatic optic neuropathy (ITON) and mild traumatic brain injury (mTBI) is based on histopathologic and optical coherence tomography (OCT) studies in the eyes and brains of rodent models.[1–5] mTBI can result in focal regions of retinal ganglion cell (RGC) loss and optic nerve damage, as detected on pattern electrophysiology and on histopathology in the rodent concussive mTBI model.[1,5] In humans with mTBI, the neurovascular injury to the eye has not been well-studied.

According to the 2017 Department of Defense Worldwide Numbers for TBI, sustained chronic mTBI comprises 84.8% of all TBI diagnosed in the OEF/OIF/OND (Operation Enduring Freedom/Operation Iraqi Freedom/Operation New Dawn) in Afghanistan and Iraq and is therefore far more common than TBI due to moderate and severe head injuries caused by penetrating bullets, vehicle accidents, and so forth.[6] Although ocular damage in eyes with closed globe injury after blast exposure has not yet been fully studied, some data show that binocular function, visual fields, and other aspects of visual function may be impaired after blast-related traumatic brain injury (TBI), despite maintenance of relatively normal visual acuity.[7] High rates of visual field deficits were demonstrated on reliable automated perimetry testing in veterans with blast-related TBI of various severities.[8]

An increasing number of veterans from recent military conflicts abroad have been diagnosed with mTBI and visual pathway trauma, especially ITON. Data on the epidemiology and natural history of visual pathway trauma in the military are currently being collected from The Defense and Veterans Eye Injury and Vision Registry, a registry for traumatic optic neuropathy that collects longitudinal clinical data on active duty service members and veterans with traumatic visual dysfunction.[9] Not only are there no detailed published data about the natural history of ITON,[9] but it is uncertain which visual biomarkers are the most reliable to monitor the evolution of this visual injury. ITON in mild chronic TBI causes afferent visual dysfunction that has been previously unrecognized on routine clinical eye examination.

In this retrospective study, we examined the clinical presentation of ITON in veterans with chronic mTBI. Using spectral-domain OCT with enhanced depth imaging, the thicknesses of the macular ganglion cell layer (mGCL), peripapillary retinal nerve fiber layer (pRNFL), and subfoveal choroidal layer were analyzed in the 38 eyes of 19 veterans with a mean age of 37.0 ± 11.8 years who had mTBI of more than 6

months' duration and either blunt head injury or improvised explosive device (IED) concussions.

Methods

Subject Selection

In this retrospective observational single-site study over a 14-month period, we analyzed data from both eyes of 19 veterans (18 males/1 female) with a mean age of 37.0 ± 11.8 years who had mTBI of more than 6 months' duration and either blunt head injury or IED concussions. The OCT data from these mTBI subjects were compared with those of four male healthy controls with a mean age of 27 ± 1years.

Study subjects who had undergone neurological and ophthalmological examinations and who fulfilled the persistent posttraumatic headache (PPTH) criteria[10] were screened for eligibility. We considered the currently available TBI screening questionnaires as insensitive and unreliable for the purposes of our study; rather, we used Department of Defense criteria for the diagnosis of mTBI in conjunction with the associated symptoms of posttraumatic headache, present in up to 90% of mTBI patients.[11] We excluded subjects with any systemic diseases, other neurological disorders, and ophthalmological disorders that would affect the OCT measurements.

Inclusion Criteria

- Male or female subjects aged ≥18 to ≤65 years.
- Diagnosis of PPTH, defined as any headache fulfilling criteria A and B:
  - A. Headache is reported to have developed within 7 days after head injury and one or more of the following:
    1. Two or more other symptoms suggestive of mTBI: nausea, vomiting, visual disturbances, dizziness, and/or vertigo, impaired memory and/or concentration.
    2. Regaining of consciousness after head injury.
    3. One of more of the following symptoms and/or signs immediately after head injury:
       - a. Transient confusion, disorientation, or impaired consciousness.
       - b. Loss of memory for events immediately before or after the head injury.
  - B. Headache persists for >3 months after the head injury.
- Adequate OCT measurements available.

Exclusion Criteria

- Headache in moderate or severe TBI associated with the following:
  - Loss of consciousness for >30 minutes.
  - Glasgow Coma Scale score <13.
  - Posttraumatic amnesia lasting >24 hours.
  - Altered level of awareness for >24 hours.
  - Imaging evidence of a traumatic head injury, such as intracranial hemorrhage and/or brain contusion.
- Migraine attack on the day of or during the OCT procedure.
- Other preexisting neurological disease that would cause structural abnormalities on magnetic resonance imaging (MRI), computed tomography (CT), or on OCT.
- Other optic nerve or retinal disease.
- Systemic diseases, such as diabetes or hypertension.
- Ocular surgeries within the past 6 weeks.
- IOP >21 mm Hg OU.
- Refractive abnormalities: Hyperopia > +5 diopters (D); myopia < −7 D, astigmatism >3 D.
- Media opacity.

To confirm that the severity of head injury was mild, 3-Tesla MRI of the brain and orbits with and without gadolinium was performed to rule out structural lesions and to confirm only metabolic hypofunction from the trauma. None of these subjects had any optic nerve, chiasmal, or posterior visual pathway abnormalities; skull, or orbital fractures.

Data Collection

The following data from the clinical history of each subject were recorded: age, sex, visual symptoms at the time of the most recent eye examination, type of mTBI (blunt and/or blast injury), year(s) when head injury occurred, results of the 3-Tesla MRI of the brain, and results of the positron emission tomography (PET) MRI of the brain.

Before data collection, each study subject underwent a complete ophthalmological examination that included the best-corrected visual acuity (BCVA) by manifest refraction, color vision screened by the 15-plate Ishihara color plates, relative afferent pupillary defect, extraocular motility, slit lamp examination of the anterior segment, IOPs measured by Tonopen, and a dilated fundus examination. Snellen visual acuity measurements were converted to a logarithmic scale (logMAR) for statistical analysis. Each subject completed a Humphrey automated perimetry (HFA model 460; Humphrey Instruments, Inc., San Leandro, CA, USA) 24-2 central threshold visual field testing. Mean deviation (MD) was used to quantitate visual field defects from each eye. Spectral-domain OCT (SD-OCT) was performed using the HRA-SPECTRALIS from Heidelberg Engineering Inc. (Franklin, MA, USA). The preset pRNFL scan consisting of a circular 3.45-mm B-scan centered on the optic nerve and a large 300 × 250-µm macular volume scan centered on the fovea was performed in all subjects. Full retinal layer segmentation was completed using the device's automated segmentation software (Heidelberg Eye Explorer software version 1.9.13.0). To detect RGC loss near the parafovea region, a modified Early Treatment Diabetic Retinopathy Study (ETDRS) grid was used, composed of three concentric rings (1 mm, 2 mm, and 3 mm) centered on the fovea. The 2-mm and 3-mm rings were subdivided into superior, inferior, nasal, and temporal sectors. The same experienced eye technician and neuro-ophthalmologist performed all eye examinations and obtained all images, including pRNFL scans, macular scans with ganglion cell layer (GCL) segmentation, and choroidal thickness measurements.

The subfoveal choroidal thickness, defined as the vertical distance from the hyperreflective line of Bruch's membrane, directly below the lowest point of the fovea, to the hyperreflective line of the inner surface of the sclera, was measured using the enhanced depth imaging OCT software.

Statistical Analyses

Based on the assumptions of statistical normality, the estimated sample size was 30 eyes (15 subjects) that would be compared with 30 eyes (15 healthy control subjects) with a significance level of 0.05, an effect size of 0.5, and a power of 0.6. After collecting the data, the actual sample size consisted of 38 eyes (19 subjects) and 8 eyes (4 healthy control subjects between the ages of 30 and 40 years recruited from the Department of Veterans Affairs [VA] hospital staff). Because the assumptions of normality for parametric tests were not fulfilled, we used nonparametric tests to analyze our data.

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Table 1. The Clinical Features of mTBI in Our Study Cohort of 19 Subjects

Age, y	Sex, M/F	Type of mTBI	Year of mTBI	Hypometabolic Regions on PET MRI of the Brain
27	M	Blast	NA	Left temporal lobe
27	M	Blast	2007	Right > left temporal lobes
29	M	Blunt	2007	Bilateral occipital lobes
31	M	Blunt	2014	Right frontal, bilateral temporal, bilateral cerebellar lobes
32	M	Blunt	1984	Left temporal lobe
33	M	Blast	2007	Left > right temporal lobes
35	M	Blunt	2000	NA
37	M	Blast	2010	NA
40	M	Blast	2007	Bilateral temporal lobes
43	M	Blast	2003	Right cerebellar lobe
44	M	Blunt	2001	Left temporal lobe
46	M	Blunt & blast	1989	Bilateral frontal, left parietal, bilateral cerebellar lobes
47	F	Blast	NA	NA
49	M	Blunt	2016	Left temporal lobe
50	M	Blast	1991	Normal
53	M	Blast	2007	Right temporal lobe
56	M	Blunt	1984	NA
64	M	Blunt	NA	Right temporal lobe
67	M	Blast	1977	Normal

Measurements were made on each eye for both those with and without mTBI. Because characteristics of the two eyes from the same individual are likely correlated, we sought to ensure independence of observations in the analyses by averaging across each subject's eyes to create a single independent measurement per subject. We first tested the validity of this step by comparing left and right eyes using a Wilcoxon signed rank test.

We then used Wilcoxon rank sum tests to determine whether any sectors of the retinal nerve fiber layer (RNFL) and GCL (temporal, nasal, superior and inferior), and at what distance from the fovea (GCL only) might differentiate those with mTBI from our control subjects. In patients with mTBI only, parallel GCL and RNFL sectors were compared using Spearman nonparametric correlation coefficients. Spearman's rank order correlation coefficients were used to compare the GCL sector thicknesses with the corresponding RNFL sector thicknesses, and to compare the subfoveal choroidal (SC) thickness with each of the GCL and RNFL sector thicknesses.

A P value less than 0.05 was considered statistically significant in all of the above calculations. In this exploratory study, no multiple comparison adjustments were made because the results are explained, not by chance, but by similar biological relationships that are found in other published animal and human studies.

This retrospective chart review study was approved by the local institutional review board with a waiver of consent at the Phoenix VA Health Care System hospital in Phoenix, Arizona. The study followed the tenets of the Declaration of Helsinki.

Results

Neurological Clinical Features

Over a 14-month period, we analyzed data from 19 postwar veterans (18 males/1 female) with a mean age of 37.0 ± 11.8 years who had mTBI of more than 6 months' duration and blunt head injury and/or IED concussions. These study subjects were compared with four healthy controls with a mean age of 26.0 ± 2.9 years.

All subjects had a diagnosis of PPTH and mTBI according to the above inclusion criteria: 10 (53%) had only blast injuries, 8 (42%) had only blunt injuries, and 1 (5%) had both blunt and blast injuries. The severity of the TBI in all subjects was mild, as previously defined. The MRI of the brain with and without gadolinium was normal in all subjects.

Hypometabolism, as detected on PET MRI of the brain, was most prevalent in the temporal lobes (53%) compared with the frontal, parietal, and cerebellar lobes (Table 1). Furthermore, all study subjects were treated with topiramate up to 100 mg by mouth every day and botulinum toxin injections every 10 to 12 weeks for migraine prophylaxis, in addition to oral sumatriptan as needed for abortive therapy.

Ophthalmological Clinical Features

At the time of the most recent neuro-ophthalmological examination, all of the affected subjects had mild visual symptoms, including blurred vision and photophobia; an additional 47% reported floaters. Characteristics of the eyes of the 19 study subjects (averaged across both eyes for each subject) were compared with those of the four healthy subjects (similarly averaged) without any systemic disorders or history of head injuries. The average BCVA was 0.068 ± 0.120 logMAR units OD and –0.042 ± 0.121 logMAR units OS in the affected group. No relative afferent pupillary defect (RAPD) was detected in any subject. In the affected group, the average IOPs were 14.5 ± 3.24 mm Hg OD and 14.3 ± 3.15 mm Hg OS. Forty-seven percent of the affected group had mild disc pallor in one or both eyes; the other affected subjects had a normal fundus. In the affected group, Humphrey Visual Field (HVF) 24-2 showed an average MD of –4.67 ± 6.61 dB OD and –4.05 ± 5.55 dB OS; superior or inferior arcuate defects, paracentral scotomas, mild peripheral depression, diffuse depression, and normal fields were also noted.

OCT Findings

There was no statistically significant difference in the inter-eye correlation for the main outcome measures of GCL, RNFL, and SC thickness measurements. The superior RNFL thickness (P = 0.02) measurement was the only variable that was statistically significantly different between the two eyes (range of 0–45 units). This difference was likely due to one eye being more affected than the other from the head trauma. Because the more affected eye of the pair from one subject could not be clinically differentiated from the less affected eye, the OCT outcome measure was calculated as an average value of the two eyes.

As measured with SD-OCT enhanced depth imaging software, the correlation between subfoveal choroidal thickness in eyes of mTBI patients and that of controls is shown in Table 2. Compared with controls, the subfoveal choroidal thickness was statistically significantly thinner in mTBI subjects (median = 211 μm; P = 0.05). The subfoveal choroidal thickness was not correlated with any sector of mGCL or pRNFL thickness.

The correlations between pRNFL thickness measurements in eyes of mTBI patients and those of controls are shown in Table 2. Compared with controls, the pRNFL in the temporal sector was statistically significantly thinner in mTBI subjects (median = 61.5 μm; P = 0.04). None of the pRNFL sectors at 2 mm or 3 mm circle diameter distance from the fovea could distinguish mTBI subjects from controls.

Table 2. Correlations Between pRNFL Thickness Measurements in Eyes of mTBI Patients and Those of Controls

Variable	Median, µm	IQR	Median, µm	IQR	*P* Value
Subfoveal choroidal thickness	369.5	(242, 523)	211	(185, 263.5)	0.05
pRNFL thickness					
Temporal	75	(73.5, 78)	61.5	(55.5, 71)	0.04
Nasal	60.5	(58, 91)	69.5	(56.5, 82.5)	0.96
Superior	120.5	(116.5, 153)	114	(97.5, 120.5)	0.17
Inferior	128.5	(109.5, 163.5)	117	(112, 128.5)	0.49
mGCL thickness					
Temporal, 2 mm	46.5	(43, 50)	44	(41, 46)	0.17
Temporal, 3 mm	52.3	(48.5, 54.8)	51.5	(44.5, 52.5)	0.31
Nasal, 2 mm	44.8	(41, 50.3)	47.5	(44, 49)	0.63
Nasal, 3 mm	56.5	(55.5, 60.8)	56	(51, 59.5)	0.63
Superior, 2 mm	53	(49.8, 54.5)	53	(47, 57.5)	0.68
Superior, 3 mm	55.8	(50.5, 60.5)	52	(44, 56)	0.16
Inferior, 2 mm	51.8	(50.5, 57.5)	50	(48, 53)	0.19
Inferior, 3 mm	52.3	(47.5, 56.5)	51	(46.5, 54.5)	0.6

The correlations between the mGCL thickness and its corresponding pRNFL layer thickness within eyes of mTBI patients are presented in Table 3. Within mTBI subjects, thinning in the nasal mGCL at the 3-mm modified ETDRS circle diameter distance from the fovea correlated with the corresponding temporal RNFL thinning ($\rho = 0.52$; $P = 0.03$). Inferior mGCL thinning at the 2 mm modified ETDRS circle diameter distance from the fovea also correlated with inferior RNFL thinning ($\rho = 0.49$; $P = 0.05$).

The correlations between the mGCL thickness of all eyes of mTBI patients and the type of head injury are presented in Table 4. The superior, more than the temporal, mGCL sectors at the 2-mm modified ETDRS circle diameter distance from the fovea were statistically significantly thinner in subjects with blunt head injury compared with those with IED head trauma (median = 48 µm; $P = 0.017$).

Discussion

ITON is the most common type of optic nerve injury, followed by chiasmal injury and direct optic nerve injury related to orbital trauma. Loss of visual acuity, variable visual field defects, afferent pupillary defect, and dyschromatopsia are the typical clinical hallmarks of ITON. Often no ophthalmoscopic signs are seen initially. After 3 to 5 weeks, this distal optic nerve injury is seen as optic disc pallor. [9] In this study on veterans, we found that chronic mTBI patients had a very mild form of ITON. Mild visual symptoms (blurred vision, photophobia, floaters, flashes) occurred in 47% of these patients, whereas the others had none. Their BCVA was often 20/20 OU. They often had normal visual fields or mild defects on Humphrey central 24-2 test and no RAPD, no color vision abnormalities, and mild or no optic disc pallor. Therefore, our findings represent the subclinical or mild end of the spectrum of ITON presentations occurring from 3 to 35 years after mTBI, the most common type of head injury in the military.

Table 3. Correlation Between mGCL and Corresponding pRNFL in mTBI Subjects Only

Sector Comparison	Rho	*P* Value
GCL-N (2 mm) × RNFL-T	0.12	0.64
GCL-N (3 mm) × RNFL-T	0.52	0.03
GCL-T (2 mm) × RNFL-N	0.11	0.67
GCL-T (3 mm) × RNFL-N	0.02	0.95
GCL-S (2 mm) × RNFL-S	0.10	0.70
GCL-S (3 mm) × RNFL-S	0.27	0.29
GCL-I (2 mm) × RNFL-I	0.49	0.05
GCL-I (3 mm) × RNFL-I	0.45	0.07

Statistical significance at $P < 0.5$. I, inferior; N, nasal; S, superior; Rho, Spearman's rank correlation coefficient; T, temporal.

In studies regarding the rates of RGC and pRNFL loss after acute traumatic optic neuropathy, ganglion cell-inner plexiform layer (GCIPL) thinning precedes pRNFL changes within 2 weeks after the trauma, and even before optic nerve atrophy ensues at 3 to 5 weeks after trauma, as shown in animal models[12] and in humans.[13,14] Therefore, RGC soma and dendritic loss precede axonal loss and optic nerve atrophy. In our study, this optic nerve atrophy, seen as mild temporal disc pallor in 47% of the eyes of mTBI patients, is represented as the statistically significantly thinner temporal pRNFL in eyes of mTBI patients compared with those of controls.

Within the eyes of our mTBI patients on Heidelberg SD-OCT, thinning in the nasal mGCL at the 3-mm modified ETDRS circle diameter distance from the fovea correlated most with the corresponding temporal pRNFL thinning. Inferior mGCL thinning at the 2-mm modified ETDRS circle diameter distance from the fovea was minimally correlated with inferior pRNFL thinning. In the study by Vessani et al.,[15] on clinically apparent ITON with or without evidence of orbital abnormalities within 3 months of blunt trauma, the superior and inferior outer GCIPL were most affected compared with other areas. Unlike the eyes with ITON with more acute and severe visual loss in the study by Lee et al.,[16] our study showed very mild RGC/pRNFL loss in eyes of chronic mTBI patients. This mild visual injury may be considered as subclinical to minimal ITON. A reduction of at least 25% of the RGC complex is required to produce a corresponding statistical abnormality on automated perimetry.[17] Although the temporal pRNFL loss correlated with the mild temporal disc pallor observed in 47% of the eyes of our mTBI patients, the MD of −4.67 ± 6.61 dB OD and −4.05 ± 5.55 dB OS on reliable HVF 24-2 tests suggests that less than 25% of RGCs died.

Inner (2 mm) superior and temporal mGCL thinning was another significant OCT finding that could distinguish eyes from patients with blunt head injury from IED concussive head trauma. Compared with the mGCL measurements at the 3-mm modified ETDRS circle diameter from the fovea, the superior, more than the temporal, sector of the mGCL at 2 mm was statistically significantly thinner in eyes of patients with blunt head injury than those with IED concussive head trauma. None of the mGCL sectors at 2-mm or 3-mm circle diameter distance

Table 4. Correlations Between the mGCL Thickness of All Eyes of mTBI Patients and the Type of Head Injury

	IED Concussive Trauma		Blunt Injury Trauma		
Retinal Layer on OCT	Median, μm	IQR	Median, μm	IQR	*P* Value
Subfoveal choroidal thickness	205	(185, 263.5)	217	(190, 320)	0.49
pRNFL thickness					
Temporal	60.8	(55.3, 74.3)	64	(52.8, 69.8)	0.79
Nasal	73	(58.8, 88.3)	65.5	(56.3, 79)	0.56
Superior	115.8	(99.8, 121)	110.5	(95.3, 121.8)	0.75
Inferior	118	(113.3, 124)	113	(111.8, 126.5)	0.67
mGCL thickness					
Temporal, 2 mm	45	(44, 46.5)	41	(38.5, 44)	0.02
Temporal, 3 mm	52	(50, 52)	46.5	(43, 52.5)	0.69
Nasal, 2 mm	48.5	(45.5, 49)	44	(41, 47.5)	0.07
Nasal, 3 mm	58.5	(56, 60)	51.5	(49, 56)	0.06
Superior, 2 mm	56.5	(52.5, 58.5)	48	(46, 53)	0.017
Superior, 3 mm	52.5	(48.5, 55.5)	50.5	(43, 56)	0.56
Inferior, 2 mm	52	(48, 54)	49	(46, 50.5)	0.06
Inferior, 3 mm	51	(49.5, 54.5)	48	(46.5, 51.5)	0.17

from the fovea could distinguish mTBI subjects from controls in our study.Therefore, these results suggest that blunt head injury is associated with more RGC loss than IED concussive head trauma. Compared with IED concussion head trauma, our study suggests that blunt head injury is associated with more eye injury, that is, parafoveal RGC loss. Because most veterans suffer from mixed blast-blunt head injury,[18] the type of head injury may not be as important as the repetitive aspect of the head trauma, which has been implicated as a more important risk factor in the development of chronic traumatic encephalopathy, a tauopathy that progresses slower than other types of dementias.[19,20] Even mild chronic mTBI without loss of consciousness was recently shown to be associated with a greater than 2-fold increased risk of dementia, based on a study of all patients diagnosed with TBI in the VA health care system from 2001 to 2014.[21]

ITON is usually a result of a frontal or midfacial trauma that may be trivial. Force from the mild head trauma is transferred from the forehead and brow to the orbital apex.[22,23] Because the intracranial portion of the nerve is relatively fixed within the bony canal, it is believed that this acceleration and deceleration of the head from blunt force can produce torque to cause stretching/shearing in the posterior optic nerve.[24] Our study results confirm that the superior mGCL thinning in our patients with ITON from chronic mild blunt head injury is similar to those with more acute ITON from blunt trauma by Lee et al.[16] This pattern of RGC loss in the superior quadrant of the mGCL, which corresponds to the superior axons of the optic nerve, is similarly observed in the eyes of patients with glaucoma[25] and Alzheimer's disease.[26] These superior quadrant RGCs injured by sustained elevated IOP in the mouse glaucoma model are mostly ON alpha RGCs[27] and may have intrinsically photosensitive properties for the detection of contrast sensitivity.[28]

Overall, the mGCL thinning demonstrated in this study represents neuronal loss from head trauma, similar to that seen on retinal histopathology and by pattern electroretinogram (PERG) in mTBI mouse models.[1,2] We confirmed that the mGCL and RNFL thinning likely represents some loss of melanopsin RGCs. The macula has the greatest density of RGCs in the retina.[29] Within the parafoveal region lie the greatest number of intrinsically photosensitive melanopsin RGCs that have non–image-forming functions of the eye, such as mediating photophobia[30] and the photoentrainment of circadian rhythms, such as sleep cycles.[31] These large RGCs, mostly M1d subtype, are most abundant 10 degrees nasal and 10 degrees temporal to the fovea. They are relatively evenly and sparsely distributed elsewhere in the retina. This cell distribution pattern in the retina is maintained with aging.[32] Unlike other types of alpha RGCs that are susceptible to traumatic axonal injury, as shown in the mouse optic nerve crush model,[33] melanopsin RGCs are relatively resistant to axonal transection or crush injury.[34,35] Our data regarding mGCL thinning suggest that they could be susceptible to direct neuronal injury from mechanical trauma. Although our results suggest that melanopsin RGCs could be proportionately more affected in the parafoveal region than elsewhere in the peripheral retina, our findings would need to be confirmed by histopathology in postmortem eyes of chronic mTBI patients. In eyes of patients with more severe chronic TBI, pupillary light response to blue light has been shown to be abnormal.[30] It has also been previously shown that at least an 80% loss of melanopsin RGCs throughout the retina is required for an abnormal pupillary response to blue light pupillometry.[36] Because of the focal loss of RGCs in the parafoveal region, testing with blue light pupillometry would unlikely produce a detectable abnormal response in the eyes of our chronic mTBI patients.

Last, ITON causes not only neuronal and axonal injury, but also impaired perfusion to the optic nerve and choroid, especially the choriocapillaris on fluorescein angiography and on indocyanine green angiography.[37] The choroid serves as the major blood supply to the retina and contributes 90% of the oxygen to the retina.[38] Compared with controls, the subfoveal choroidal thickness was statistically significantly thinner in mTBI subjects (median = 211 μm; $P = 0.05$), as measured with SD-OCT enhanced depth imaging techniques. The subfoveal choroidal thickness was also not correlated with any sector of GCL or RNFL thickness. Unlike choroidal thickening after acute ITON within 2 weeks of blunt trauma,[39] we showed subfoveal choroidal thinning in chronic subclinical ITON. In the more acute stages of ITON, there is increased venous pressure causing increased permeability of the choriocapillaris that can sometimes lead to choroidal artery occlusion after the fourth day post-trauma.[40] In contrast, the subfoveal choroidal thinning in our study could be a result of atrophy from vascular injury after head trauma.

Some limitations were encountered in this study. The median age of the control group was approximately 10 years younger than that of the study group, and the number of controls was far fewer than the anticipated sample size calculation because older healthy veterans at our study site were not available. The sex of the control group was all male

and that of the study group was all male, except for one female. Although this was a single-center retrospective study with a small sample size and a limited number of healthy controls, we were still able to detect a statistically significant traumatic injury effect on the retina. The pattern of RGC loss in ITON was similar to that in glaucoma[25] and in Alzheimer's dementia.[26] These findings will obviously need to be confirmed in a prospective study with a larger sample with the appropriate age- and sex-matched controls for not only statistical significance, but for practical significance. Although our exploratory study focused on inner retinal structural injury, pattern electroretinogram also will be considered to assess for RGC dysfunction.

Furthermore, differentiating pRNFL and choroidal thinning in mTBI from that related to migraine was not possible in our study cohort. The diagnostic criteria of mTBI with posttraumatic headache was chosen because it is a more common clinical presentation and a more debilitating form of chronic mTBI compared with that without headaches.[11] Based on the current literature, the pRNFL and mGCL measurements in migraine patients have been very inconsistent. Some studies have found statistically significant diffuse thinning in the mGCL and/or pRNFL in the eyes of migraine patients compared with that of controls, whereas others have found thinning in only certain mGCL and/or pRNFL quadrants.[41–44] Despite the possible effects of migraine on our measurements of mGCL and pRNFL, our findings of sectoral mGCL and pRNFL thinning are consistent with those in other ITON studies.[16,45] Furthermore, numerous studies on choroidal thickness in migraine also have been inconsistent, with some showing increased choroidal thickness, and others showing reduced thickness.[46–48] Because of the vasoactive effects of migraine and migraine medications on the choroidal layer thickness measurements, we minimized these effects on our data by treating all of our mTBI patients with the same medications (topiramate, sumatriptan, and botulinum toxin injections); and including only those without a migraine attack on the date of, or during, the OCT scan procedure. Retinal blood flow studies might be a better method to assess vascular damage and perfusion in future studies.

Conclusions

In conclusion, this study describes the OCT pattern of neurovascular injury in the eyes of veterans with chronic mTBI. We have described a subclinical or mild presentation of ITON that occurs in veterans exposed to blast and/or blunt head injury. This visual injury in mTBI is different from that seen in the classic ITON in the civilian population with mTBI from only blunt injury. Our OCT data were obtained in the eyes of veterans diagnosed with TBI of mild severity. The mild category was defined not only by clinical criteria with a normal brain CT and MRI, but was also confirmed with brain PET MRI.

In this study, three major OCT findings were demonstrated in the eyes of chronic mTBI patients: (1) temporal pRNFL thinning was associated with subclinical ITON compared with controls; within mTBI subjects, thinning in the nasal mGCL at the 3-mm modified ETDRS circle diameter distance from the fovea correlated with the corresponding temporal RNFL thinning; (2) in the 2-mm circle diameter of the modified ETDRS grid, the superior more than the temporal sector of the mGCL was statistically significantly thinner in eyes of patients with blunt head injury and could reliably distinguish blunt head injury from IED concussive head trauma; and (3) subfoveal choroidal thinning was significantly thinner in eyes of mTBI patients compared with those of controls.

Understanding the evolution of the pathophysiology of retinal and optic nerve damage from head trauma on a cellular level and identifying reliable clinical biomarkers for the early detection of mTBI will allow the implementation of novel neuroprotective strategies. Persistent cellular inflammation after the acute injury is thought to worsen and contribute to further neurodegeneration, so that chronic visual deficits present months to years after the acute head injury.[49,50] Some rodent mTBI models in the chronic stage even show evidence of tau and beta-amyloid deposition in the optic nerve on histopathologic sections.[50] Whether the anterior and/or posterior visual pathways continue to undergo a similar chronic phase of neurodegeneration as a tauopathy remains to be fully elucidated. A better understanding of which RGC type and subtypes are most susceptible to mechanical injury also will help in developing specific RGC replacement and neuro-regenerative therapies for visual restoration in the subcortical and cortical visual pathways.

Acknowledgments

The authors thank Ross Aichele for excellent ophthalmic technical assistance.

Supported by the Clinical and Translational Sciences Institute grant at University of California, San Francisco, and the Kuen Lau Research Foundation.

Disclosure: **J.W. Chan**, None; **N.K. Hills**, None; **B. Bakall**, Spark Therapeutics (C); **B. Fernandez**, Heidelberg Engineering (E)

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