1874-3641/23

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REVIEW ARTICLE

Ophthalmic Manifestations, Evaluation, and Guidelines for Testing of Concussion

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Abstract:

Early detection and treatment of concussions is crucial to preventing further brain damage. Current subjective standard-of-care tests used to diagnose concussions, such as symptom reporting and standardized concussion checklists, can often underdiagnose patients with concussions. This review will cover novel biomarkers of concussions related to concussion-associated visual deficits and how they can be used to more accurately monitor patient concussion symptom improvement. Visual deficits are seen in up to 90% of patients within hours after a concussion-inducing trauma and can serve as objective biomarkers in diagnosing and monitoring concussions. Some of the key visual deficits that are seen in patients with concussions include convergence insufficiency, problems with accommodation and smooth pursuit of eye movements, saccade dysfunction, and decreased optokinetic nystagmus gain. Patients frequently report blurred vision, difficulty reading, double vision and eyestrain, dizziness, visual field defects, and light sensitivity related to concussions. Promising eye tests to detect and track concussions include pupillary light reflexes, the circle test, and the Samandarani group's non-spatially calibrated binocular motility test/algorithm in conjunction with video oculography and eye tracking equipment. The EYE-SYNC eye-tracking device allows for portable and accurate detection of eye movements in the field and is a promising tool for detecting concussions both in the field and clinic. Optical coherence tomography and other retinal imaging modalities also represent a promising method of identifying individuals who have sustained a concussion.

Keywords: Concussion, Traumatic brain injury, Visual symptoms, Accommodation, Nystagmus, Convergence insufficiency, Saccades, Smooth pursuit movements, Concussion evaluation testing.

Article History	Received: August 9, 2022	Revised: December 21, 2022	Accepted: December 23, 2022

1. INTRODUCTION

A concussion is a mild traumatic brain injury (mTBI) and results from trauma to the head or body, leading to either a loss of consciousness, memory, altered mental status, or neurological signs [1]. Concussions typically resolve within several weeks of the injury [2 - 5]. More serious sequelae can occur when the diagnosis is missed, and a second head injury occurs.

Several estimates based on emergency room admissions have shown that the incidence of concussions is about 3.8 million annually in the US [6 - 8]. However, the true concussion incidence is likely much higher than what is reported since many athletes continue to compete after sustaining a concussion and do not realize the extent of their injury [9]. Many sports-related concussions are diagnosed subjectively utilizing symptom checklists, standardized assessments of balance, sports concussion assessment tools, and the King-Devick test [10]. It is critical, however, to provide objective and accurate methods of detection of concussions to prevent the potentially serious complications of repeated concussions, including second impact syndrome, which can lead to life-threatening brain swelling [11]. In addition, repeated mTBI acutely can lead to longer recovery times and more severe physiological effects and neurocognitive outcomes [12, 13]. Chronic repeated concussions may result in cognitive dysfunction and even neurodegeneration [14].

In addition to neurological dysfunction, concussions, especially when repeated, can result in visual dysfunction. Even five years after experiencing mild TBI (concussion), veterans from the wars in Iraq and Afghanistan reported visual symptoms associated with the initial concussion [15]. In fact, between 40% and 90% of individuals with acquired brain injuries have eye movement deficits [16 - 18]. Visual symptoms are frequently seen in patients with concussions because over half of all brain circuits involve vision and eye movement [19]. Brain areas that regulate proper eye movement, such as the frontal lobe, parietal cortices, and subcortical nuclei, are particularly susceptible to damage from

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DOI: 10.2174/18743641-v17-e230111-2022-43, 2023, *17*, e187436412301050

concussions [20, 21].

Due to the clinical relevance of eye findings in concussions, ophthalmic screening is an effective method for diagnosing and evaluating the progression and severity of patients presenting with concussions, due to their objective nature and potential ability to serve as concussion biomarkers. This paper describes the ophthalmic symptoms and signs associated with mild traumatic brain injuries (TBIs). Ophthalmologic testing and devices used to diagnose concussion are reviewed and evaluated for effectiveness and accuracy. Future modalities to identify early mTBI are reviewed.

2. METHODS USED FOR EVALUATING REFERENCES

A PubMed and Google Scholar search was done to find recent experimental research studies, case reports, and review papers on the topics of concussion, ophthalmic manifestations, and new technologies and screening methods. First, a search was done for current methods of concussion screening to evaluate the efficacy and accuracy of current tests, as well as to summarize the standard of care practices being used both in the clinic and on sports fields. Then, further searches were done to evaluate the most objective and accurate ophthalmic tests for concussion screening, with particular emphasis on new methods and screening techniques that have been used within the past five years. To evaluate the references, further searches were done on the techniques and devices reported to evaluate responses and criticisms, and the efficacy values of contrasting methods. Then based on those findings, more literature review was done showing links between concussion manifestations and optical coherence tomography, retinal imaging, as well as EYE SYNC, to further evaluate new approaches to accurately diagnosing concussions both in sports/field settings and in clinic settings that are not currently implemented but hold promise as diagnostic methods for the future.

3. OPHTHALMIC MANIFESTATIONS OF CONCUSSION

Typical eye findings associated with concussions include convergence insufficiency, accommodation deficits, smooth pursuit abnormalities, saccadic dysfunction, and decreased optokinetic nystagmus gain [8, 10, 20, 22 - 25]. These deficits often result in symptoms of diplopia, decreased visual attention, blurred vision, asthenopia, ocular pain, and difficulty with accommodation, photophobia, abnormalities of color perception, pupillary abnormalities, abnormal eye tracking movements, and potential visual field defects [20, 26 - 28]. Despite large variability in the causes and degrees of traumatic brain injury, the incidence of visual symptoms in patients with concussions remains consistent and trackable over time [20, 26]. Examination of an acutely concussed patient should include near and distance acuity, identification of anisocoria, vestibulo-ocular reflex defects, slowed and reduced eye movement, convergence and/or accommodation defects, and assessment of peripheral visual fields [20, 29].

Accommodation involves focusing the eyes on a near object. This mechanism requires neural input from the visual cortex, brainstem, and ciliary muscles, and due to the large number of complex pathways involved, accommodation is highly susceptible to damage from trauma [20]. Clinical features of problems with accommodation include blurred vision, asthenopia, and difficulty seeing small print [28]. Across pediatric and adult populations, individuals with concussions had a significantly reduced capacity for accommodation [30]. A confounding factor for errors with accommodation is myopia, since there is commonly an accommodative lag with these patients [20].

Convergence is the inward movement of the eyes to maintain a binocular fixation on an object. This ability involves the visual cortex, parietal lobe, frontal eye fields, supra-oculomotor area and cerebellum [20]. The clinical manifestations of convergence dysfunction in patients with a concussion include double or blurred vision with prolonged close-up tasks [27, 31, 32]. 14-55% of patients with concussions have convergence abnormalities for at least a month after a mTBI [15, 27, 31 - 36].

Saccades are rapid eye movements between two fixation points, and abnormalities in saccadic eye movements may be the result of damage to the parietal, frontal, temporal, and caudate brain regions [37]. Up to 30% of patients that have concussions have saccadic dysfunction [27, 30, 33]. Compared to healthy controls, patients with concussions make more saccadic eye movements to complete number-naming tasks [38]. Furthermore, patients had impairments related to cortical saccadic tasks, particularly with memory-guided saccades and anti-saccades [39, 40]. Patients with a longer recovery time had greater saccadic dysfunction and made significantly more errors performing memory-guided saccades and anti-saccades that require high cognitive function [8, 41 - 43]. Patients with concussions also made significantly more position errors during memory-guided saccade tests [42, 43]. Some clinical manifestations of saccadic dysfunction include the increased time between target presentation and the start of the saccade, as well as dysmetria, resulting in difficulties reading and driving [20, 39, 40].

Smooth pursuit movements are used to keep an image steadily on the fovea [20]. Because this is another ocular movement that integrates many different regions of the brain, it is also susceptible to dysfunction from concussion. Patients with concussion experience difficulty following moving objects [29, 30]. In particular, patients have decreased target position, eye position errors, and low velocity gains, and their gaze trajectory is uneven when moving to a target. Visual tracking, which is the combination of smooth pursuit and saccadic eye movement that gives rise to visual stability and continuous observation of targets, is also impaired in patients with concussions [10].

Chronic mild traumatic brain injury has been demonstrated to lead to progressive neural degeneration demonstrated by retinal nerve fiber layer (RNFL) loss on Optical Coherence Tomography (OCT) in athletes and veterans [44, 45]. Mice with repeated mTBI exhibited decreased optic nerve diameter, and increased cellularity and demyelination compared to healthy controls [46]. Additionally, there were regions of decreased retinal ganglion cell layer and thinning of the inner retina [46].

In a study done of Division I football players that had sustained previous concussions, the retinal nerve fiber layer (RNFL) and the ganglion cell complex (GCC) both thickened, possibly as a result of immunological response and gliotic scarring [47, 48]. On the other hand, other studies have demonstrated RNFL thinning in athletes playing contact sports, as well as patients with Alzheimer's Disease, suggesting RNFL damage [49, 50]. A study of retired Australian professional rugby league players demonstrated RNFL changes correlated with cerebral white matter loss and neurodegeneration [49]. Additionally, a study of Olympic boxers demonstrated RNFL thinning as compared to healthy controls [51].

Some rare and more serious visual disturbances related to traumatic brain injury include visual field anomalies such as homonymous hemianopia and quadrantanopia or cranial nerve palsy which could present as frank strabismus or more subtle diplopia in different fields of gaze [20, 26].

4. CURRENT METHODS FOR DETECTING CONCUSSION

There are some currently established eye tests that are used in diagnosing concussions, such as the King-Devick test (K-D test). Other tests and diagnostic tools that are in development and are showing promise include video oculography and eye tracking.

The King-Devick (K-D) test evaluates eye movements while subjects have to read a series of numbers on scorecards as quickly as possible, minimizing the number of errors that they make [52]. The K-D test has high test-retest reliability and has been shown to accurately identify concussions in boxers and mixed martial arts fighters [52, 53]. For this test, patients read single-digit numbers aloud on test cards, and the time it takes to read all the numbers and the number of errors is recorded. When performing this test on the sidelines for football players before the season and after the season, individuals with no concussion had a 0.72 second improvement while subjects with concussions had a 5.9 second increase in their K-D time [52]. Individuals with concussions showed improvements in their K-D time score immediately after a two-hour scrimmage which suggests that this test is situationally-dependent to a degree [52]. The advantage of this test is its portability and adaptability for use in any environment. The disadvantage of this test is that it has approximately 75% sensitivity in detecting concussions, so it cannot be used alone to diagnose the condition [10, 53] or relied upon to determine if a player should be allowed to continue to participate in the athletic event.

Video oculography is a non-invasive technique that typically uses infrared cameras on a head mount to measure horizontal, vertical, and torsional eye movements, and can track pupils and corneal reflection [54]. This has proven to be an effective method for tracking visual symptoms associated with concussion, such as smooth pursuit and saccade deficiencies. Simultaneous measurements of pupils and corneal reflection have been validated as a biomarker for anticipatory neural activity, and can be useful in measuring visual tracking ability in patients with concussions [10, 55, 56]. This can be done by having patients look at a circular trajectory because of its predictable path while tracking their eye behavior [10]. This test is able to show concussion-associated defects in smooth pursuit tracking, increased reaction times and lower saccade velocities, decreased optokinetic nystagmus gain, phase error, root-mean-square error, as well as the variability in gaze position [23, 57, 58]. Visual tracking metrics had correlations up to 0.68 with concussion survey metrics that are the current standard of diagnosis for up to two weeks after the initial mTBI [59].

Video oculography is also used to track disconjugate gaze, as individuals with chronic symptoms of concussion have a significant decline in visual tracking abilities [55, 57]. The dysfunctions seen using video oculography were correlated with diffusion tensor imaging that showed white matter tract damage in the corona radiata and genu of the corpus callosum, which further correlated with attentional and working memory problems [10, 58].

The EYE-SYNC device has been commercialized for concussion detection, and it is able to quantify the dynamic visuomotor synchrony (DVS) of individuals' gaze with the target during the predictive circular tracking task [55, 57]. Simultaneous measurements of pupils and corneal reflection have been validated as a biomarker for anticipatory neural activity, and can also prove to be useful in measuring visual tracking ability in patients with concussions [10, 55, 56] After developing the standard values and tracking longitudinal data for individuals for the EYE-SYNC, the Maruta group also showed a significant decline in DVS in patients that had concussions within two weeks of testing, and these DVS scores returned to normal values as patients recovered [56, 59]. However, studies with larger sample sizes will help to fully validate this technique.

Eye tracking helps detect saccadic and pursuit deficits that are often missed during complete eye examinations. Eye tracking can detect abnormal eye movements within several hours after a concussion and shows a worsening deficit for 1-2 weeks after injury but then an improvement and a gradual recovery over approximately one month [43, 60, 61]. However, some studies suggest that even six months after a concussion, individuals may have some saccadic and visual pursuit deficits [8, 42].

The Samandani group developed a non-spatially calibrated binocular motility test/algorithm that is able to detect disconjugate gaze in patients with concussions [60]. This new algorithm minimizes the limitations seen from previous eye tracking tests that were spatially calibrated, such as subject fatigue, misleading results due to visual and attentional deficits, and distraction [60, 61]. Patient levels of horizontal dysconjugacy correlated well with standard concussion metrics such as SCAT-3 and SAC scores, and went back to baseline after patients recovered [60]. In follow-up studies, this algorithm was shown to have 88% sensitivity and 87% specificity for identifying concussion [62]. However, there are criticisms from other groups that ocular disconjugacy is difficult to measure with spatially calibrated eye tracking equipment [63].

The smooth pursuit test and reflexive saccade tests were commonly used to evaluate concussions through eye-tracking equipment [43]. Areas of the brain that are involved in attention and executive function help regulate both of these types of movements. Additionally, the proportion of position errors an individual makes during a memory-guided saccade test is a sensitive enough measure to distinguish between patients who were suspected to have a concussion from healthy controls [42, 43]. This test involves the hippocampus and cerebellum as well as the ventral visual pathway, and it is possible that these eye findings occur due to individuals being unable to maintain a high cognitive load due to errors in encoding and retrieving information [43, 64].

Pupillometry can be effective in measuring both accommodation and convergence deficits in patients with mTBI. Pupil constriction percentage, constriction and dilation velocity, and peak dilation and constriction velocity were all significantly altered in patients exhibiting concussions [65, 66].

Accommodation can be tested both with specialized ophthalmic equipment such as the RAF Rule (for values of amplitude of accommodation) and by bringing text closer to the subject until it becomes blurry, and comparing that distance with healthy age-matched metrics [20]. Current clinical tools to measure accommodation, however, have several confounding errors related to reaction times, instrument design, refractive errors, and psychological factors [67]. Convergence is often tested by bringing an object closer to a patient's eye, and clinicians will look for breaks in binocular fusion as seen as a divergence of an eye from the target or from a patient reporting diplopia [20]. It is possible to test saccadic eye movements by having patients move their eyes between two close targets, and a secondary eye movement adjustment suggests saccadic dysfunction [20]. However, saccades can be further evaluated using eye tracking equipment [66, 67], head-mounted saccadometers [68], or electrooculography, although this test has, for the most part, been replaced by video oculography [69 - 71]. The K-D test can also measure saccades, cognition, and attention abilities, and is typically used on the sidelines in sports. Smooth pursuit movement can be evaluated by having patients track an object across vertical and horizontal planes and measure the presence of any jerky movements or failures to follow the target.

5. FUTURE RETINAL TESTING MODALITIES

Future modalities to detect traumatic brain injury include retinal imaging techniques. Retinal OCT may serve a useful purpose in the evaluation of concussions, both acute and chronic. Overall retinal nerve fiber layer loss is evident in veterans who have undergone traumatic brain injury [44]. OCT abnormalities are detectable in up to 53% of patients with mTBI that do not have any other visual deficits [45, 48]. Furthermore, since there is a correlation between retinal nerve fiber layer thinning shown on OCT with cerebral white matter loss on MRI, it is possible that OCT can be useful for monitoring the severity of a patients' neurodegeneration as a result of repeated TBIs [49, 72, 73]. Veterans with chronic mTBI showed peripapillary retinal nerve fiber layer thinning related to traumatic optic neuropathy, as well as subfoveal choroidal thinning and retinal nerve fiber layer thinning [45]. More objective studies tracking patient concussion recovery course with OCT imaging is needed to evaluate more precise tissue changes using this modality, though.

Electroretinography of mice with repeated mTBI models has also shown a decrease in photopic negative response amplitude with no changes in timing or a and b wave amplitude [46]. Patients with mTBI and sports concussions show abnormal findings in the acute and nonacute injury stages [74]. In another study, there was a decrease in the OP3 component of ERG in a mouse model of repeated TBI which is possibly due to optic tract damage, though no other ERG changes were apparent in the mTBI mouse model [75]. Patients with mTBIs lacked photopic negative responses that were seen in ERGs from control patients, which suggests reduced plexiform layer function [76]. Furthermore, patients showing light sensitivity as a result of concussions showed shifted rod b-wave latency [76].

Additionally, retinal vessels serve as a marker of cerebral vascular changes, and there is evidence of an association between head injury and wider mean retinal venular caliber, as measured with Fundus photographs and computer-assisted techniques [77]. However, more studies are needed to validate these findings. Other modalities to evaluate the retinal vasculature may also be a future consideration, as studies have demonstrated TBI to be associated with quantifiable changes in the retinal vessels, including increased arterial and venous tortuosity [78].

6. CONCUSSION TESTING RECOMMENDATIONS

To diagnose a concussion in the clinic, key recommendations include oculomotor, neurocognitive, pupillometry, and tracking retinal manifestations of concussions. A non-spatially calibrated binocular motility test to detect disconjugate gaze developed from the Samandani group can help track oculomotor dysfunction. Smooth pursuit and reflexive saccade tests using eye tracking equipment can measure simultaneous pupil and corneal reflection to detect delays with anticipatory activity and neurocognitive activity. The EYE-SYNC device, which is practical for use outside the clinic, can also help detect neurocognitive changes correlated with anticipatory activity. Video oculography and pupillometry can aid in detecting accommodation and convergence deficits, as well as smooth pursuit tracking errors, increased reaction times, lower saccade velocities, decreased optokinetic nystagmus gain, phase error, and root-mean-square error that are all associated with concussion-related defects. Additionally, ERG testing is an effective way of detecting functional deficits in retinal activity associated with concussions, such as decreases in the OP3 component of ERGs.

This article evaluated the current diagnostic knowledge in the field related to ophthalmic manifestations of concussions and synthesized recent findings in the field to develop guidelines for the most accurate and efficient ophthalmic testing both in the clinic and outside of the clinic. This review also emphasized novel approaches that can more objectively track ophthalmic and neurological changes related to concussions. This review synthesized previous findings to more accurately diagnose concussions and create a new set of recommendations for methods to best evaluate concussions. This paper was a review and synthesis of literature and did not include any retrospective or prospective experimentation in relation to the new set of diagnostic criteria for concussions and how it differs from current standard-of-care methods. The literature reviews and methodologies in this paper solely relied on the data reported from a conglomeration of studies related to the ophthalmic manifestations of concussions.

CONCLUSION

Concussions are a frequent result of head trauma and are particularly common with sports related activities that involve direct blows to the head. Although most signs and symptoms of concussions resolve in several weeks, a second concussion in the early phase can lead to a serious condition such as second impact syndrome, which can lead to life-threatening brain swelling, brain herniation, and death [79, 80]. In addition, repeated concussions can result in chronic neurodegenerative disease.

Thus, in a setting where a person experiencing head trauma may be exposed to a further head injury (especially in the setting of an athletic event), there is a need for methods to quickly, accurately, and correctly identify those individuals who have sustained a concussion. In such a manner, the risk of second impact syndrome can be reduced by quick identification of a concussion and proper restriction of further impact to the head.

This paper has demonstrated that ophthalmic presentations of signs of concussion are frequently present, including convergence insufficiency, accommodative defects, smooth pursuit abnormalities, and saccade dysfunction. We have also reviewed some of the current methods to detect ophthalmic signs of concussion, including examination by a trained professional, the King-Devick test, video oculography, the EYE-SYNC device, pupillometry, and the Sanaandani group binocular motility test. Future possibilities of retinal OCT, ERG, and retinal vascular imaging are being studied. It is important to be able to perform this testing on the field and off the field to correctly identify individuals who should immediately refrain from the possibility of a second impact along with its potential devastating consequences.

LIST OF ABBREVIATIONS

mTBI	=	mild Traumatic Brain Injury
RNFL	=	Retinal Nerve Fiber Layer
GCC	=	Ganglion Cell Complex
DVS	=	Dynamic Visuomotor Synchrony
K-D test	=	King-Devick test
OCT	=	Optical Coherence Tomography

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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