LEARNING OBJECTIVES

1. List the common clinical neuro-ophthalmologic signs in traumatic brain injury (TBI)
2. Recognize the difficulties and controversies surrounding clinical evaluation of ocular motility in concussion (mild TBI) and post-concussive syndrome
3. Critically analyze quantitative ocular motor literature on abnormal saccades in concussion

CME QUESTIONS

1. What is the most common neuro-ophthalmologic sign in concussion?
   a. convergence insufficiency
   b. abducens palsy
   c. slow saccades

2. Which saccade type is predominantly controlled by the frontal lobes?
   a. express saccades
   b. memory-guided saccades
   c. reflexive saccades

3. Which of the following have most often been reported as abnormal in concussion?
   a. antisaccades
   b. reflexive saccades
   c. quick phases of optokinetic nystagmus

KEYWORDS

1. Concussion
2. Convergence Insufficiency
3. Antisaccades
4. Memory-guided Saccades
5. King-Devick Test

INTRODUCTION

Concussion, a major societal concern, results from biomechanically-induced alteration of brain physiology. Underlying cerebral dysfunction is primarily manifested through clinical symptomatology and standard methods of assessment for structural pathology (clinical examination and neuroimaging) are often unrevealing. The ocular motor system is governed by a complex and delicate network of cortical and subcortical structures. Given its widespread distribution, including a high load of circuitry in the frontal lobes which is prone to injury, it is highly likely to be affected by concussion. Resulting ocular motor dysfunction, particularly of saccade subtypes may, indeed, prove to be a sensitive measure of detection, a marker of biological injury, a sensitive outcome measure for clinical trials, and possibly a predictor of recovery.

INTRODUCTORY OVERVIEW: CLINICAL EFFERENT DYSFUNCTION IN TRAUMATIC BRAIN INJURY (TBI)

Ocular motor deficits are a common result of traumatic brain injury of any degree, from mild to severe, and can span the range of localizations from extraocular muscle involvement due to orbital trauma to intracranial cortical supranuclear dysfunction due to hemorrhage or diffuse axonal injury. Studies have varied in their inclusion criteria with regard to visual symptoms and severity of head injury, the overall focus of the study (all ocular involvement versus only neuro-ophthalmic versus only afferent or efferent dysfunction), the duration between injury and examination, and the presence or absence of other neurological or neuroimaging defects. Despite this variability, there is general consensus that ocular motor cranial nerve palsies are the most common efferent neuro-ophthalmologic defect in head trauma, with oculomotor (third) and trochlear (fourth) nerve involvement more common than abducens (sixth) nerve involvement. Ocular motor cranial nerve injury is typically followed in frequency by convergence insufficiency of presumed supranuclear origin.
EFFERENT DYSFUNCTION IN MILD TBI: THE CLINIC

Detailed neuro-ophthalmological studies evaluating the frequency of ocular motor deficits in patient populations with isolated mild TBI are limited; however conclusions can be drawn from broader neuro-ophthalmologic studies in generalized TBI cohorts ranging from mild to severe. Oculomotor (third) nerve paresis and multiple simultaneousocular motor nerve injuries have been associated with more severe head injury as determined by other neurological or neuroimaging deficits, such as corticospinal tract injury, intracranial hemorrhage, or basilar skull fractures. The presence of ocular motor nerve involvement, in general, is also associated with more severe head trauma as judged by lower initial Glasgow Coma Scale scores, higher rates of neuroimaging abnormalities, and higher frequency of inpatient rehabilitation. In contrast, convergence insufficiency and isolated ocular motor cranial neuropathies can occur in the setting of mild TBI, especially unilateral abducens (sixth) and unilateral or bilateral trochlear (fourth) nerve paresis.

The majority of the information discussed so far is derived from studies performed between the 1980’s and the early 2000’s in the neuro-ophthalmology or ophthalmology clinical setting, with motor vehicle accident and assault as the two most common mechanisms of injury. A shift in the origin of clinical publications of ocular motor and visual assessment in TBI has occurred over the past decade, as attention has been drawn in clinical settings and in the media to military and sports populations experiencing prominent visual symptoms following TBI, including in large populations with mild TBI / concussion. These later publications based in the optometric and rehabilitation literature are summarized here.

This body of literature often refers to a “post-trauma vision syndrome” after TBI, in which “visual imbalances can occur between focal and ambient visual processes that can affect balance, posture, ambulation, reading, attention, concentration, and cognitive function in general.” In 2007, initial reports of military patient evaluations in inaugural Veterans Affairs inpatient Polytrauma Rehabilitation Centers (PRC) and outpatient Polytrauma Network Site (PNS) clinics were published. PRC patients typically had multiple and life-threatening injuries. In contrast, PNS patients were diagnosed with mild TBI, usually associated with a blast event. Updated results of 108 PRC and 125 PNS patients were published in 2009. These programs, devised to meet the needs of Iraq and Afghanistan conflict combat survivors, many of whom sustained blast exposures and suffered from emotional trauma and physical injuries, revealed a high prevalence of TBI and post-concussion symptoms. In addition, via initial optometric visual screening processes, they had a high burden of visual symptomatology. A questionnaire assessment of visual clarity, photosensitivity, binocularity, and visual and cognitive symptoms during reading revealed a high burden of visual symptoms in 75% of patients, including prominent photosensitivity. Further, examination of visual function in these studies, including oculomotor range, binocular alignment, convergence, saccades, and smooth pursuit resulted in report of oculomotor dysfunction in the majority. The breakdown was as follows: convergence dysfunction in 40-48%, pursuit and/or saccadic dysfunction in 23-29%, strabismus in 6-19%, and fixation insufficiency in 7-13%. Ocular motor deficits were similar between the inpatient PRC and outpatient PNS cohorts, with exception of more frequent diplopia in the inpatient cohort. It was determined likely that disorders of binocular visual function may account for self-reported reading difficulties in 57-63% of the patients, though it is acknowledged in these papers that cognitive, perceptual, or attentional factors may also play a role in symptom burden. It is further noted that vision therapy is frequently employed to address functional deficits, along with visuospatial training and techniques to improve scanning and perception.

A four-tiered optometric approach to evaluation of visual issues in mild TBI has been proposed to include 1) the basic optometric vision examination (e.g., refractive status, binocular status, ocular health status), 2) oculomotor-based vision problems (e.g., fixation, saccade, pursuit, vestibular, optokinetic systems), 3) non-oculomotor-based vision problems (e.g., shift in spatial ‘sense of straight ahead’, photosensitivity, motion sensitivity, dizziness, visual information processing dysfunction), and 4) non-vision-based problems (e.g., depression, cognitive and behavioral issues, postural problems). Ocular motor deficits similar to those seen in military populations by optometrists have also been reported in civilian populations with TBI who have undergone optometric assessment.

A high prevalence of mild convergence insufficiency is found across neuro-ophthalmologic, optometric, and rehabilitation literature in mild TBI in civilian and military populations. Outside of this uniform feature, several controversies have arisen with regard to the inter-relationships between visual symptoms and examination findings. First, there are likely to be differing opinions with regard to how much visual and physical symptomatology directly relate to convergence insufficiency. It has been suggested that convergence insufficiency may result in blurred vision, diplopia, eyestrain, headaches, loss of concentration, having to reread or read slowly, difficulty in remembering what was read, and visual fatigue. Some of these are classic symptoms of convergence insufficiency, but others could originate from headache disorders or other neurocognitive or psychiatric issues triggered by mild TBI, as similar visual symptoms may also be present in mild TBI patients who lack convergence insufficiency. Second, controversy exists with regard to the frequency and significance of non-vergence dynamic ocular motor abnormalities, most notably of saccades. With regard to saccades, it has been published that assessment may be labelled as abnormal if the saccades do not appear smooth.
and accurate or if the subject is unable to perform the task. However, given the visual and physical discomfort elicited by the ocular motor examination in many mild TBI patients, there is no evidence that inability to comply with testing indicates true saccadic dysfunction. Assessment for mild saccadic dysfunction and determination of its significance at the bedside is clinically challenging. Studies to date in the Veterans Affairs PRC and PNS patient populations now report a frequency of pursuit or saccadic dysfunction ranging between 5 to 60%, with low and high percentages found in both more severe PRC populations and in milder TBI PNS populations. This may reflect the presence of different study populations in each publication, but variability could also exist due to differences in inter-examiner determination of whether a clinical saccade is normal or abnormal. Further underscoring this possibility is the fact that, despite evidence of impaired saccadic behavior in mild TBI in an ocular motor laboratory setting, studies have shown that these subjects have no abnormalities of saccades on clinical examination.

Third, there is a large discrepancy between the prominence of visual symptomatology in mild TBI and the frequency of abnormalities on clinical visual and ocular motor assessment. This had led to assumptions that elicitation of visual and physical symptoms by the ocular motor examination implies corresponding ocular motor deficits on examination, which may not be the case in many patients with mild TBI.

EFFERENT DYSFUNCTION IN MILD TBI: THE EYE MOVEMENT LABORATORY
Ocular motor recordings allow quantification of various saccade behavioral features, such as latency (time between target onset and saccade onset), velocity, amplitude, duration, accuracy, directional errors, and positional errors. Outside of the laboratory and in simplistic terms, we typically utilize two main types of saccades: volitional purposeful saccades that are largely governed by frontal lobe saccade centers and reflexive saccades that are largely governed by parietal saccade centers. In the laboratory, in addition to studying volitional and reflexive saccades as broad categories, saccade behavior can be altered via manipulation of the timing of onset and offset of fixation and saccade visual targets. A number of other saccade types can then be generated in a controlled setting. Comprehensive coverage of this topic is far beyond the scope of this syllabus, but a few saccade types heavily utilized in mild TBI research will be briefly described. These include memory-guided saccades, antisaccades, self-paced saccades, and reflexive saccades (Table 1). Smooth pursuit and vestibular eye movements have also been studied in mild TBI, but the discussion here will be restricted to saccades.

Before compiling the research results, it is worthwhile to ask the question why is it worth it to study detailed saccade behavior in the laboratory in mild TBI? There are at least four important answers to this question: 1) improved detection of structural injury in highly symptomatic patients with a heavy burden of visual and other symptomatology, 2) exploration of underlying neuroanatomic deficits, 3) for potential future use as outcome measures in clinical trials, and 4) as potential markers for assessment of recovery. Patients who sustain mild TBI may develop a protracted post-concussive syndrome, with few to no findings on standard physical examination and brain MRI. As has been seen in multiple studies in the above clinical section, the majority of these patients have a very high burden of incompletely understood visual symptoms. Further, physicians may be biased towards the possibility of secondary gain in the form of disability or litigation as the most prominent mechanism underlying post-concussive deficits. While this may be true in some individuals, studies assessing this question have found a minimal role of secondary gain in patient outcomes and organic injury likely due to diffuse axonal injury can be identified with more detailed evaluation methods, such as neuropsychological testing, positron-emission tomography and functional MRI, and via ocular motor recordings.

Table 1. Examples of Saccade Types

<table>
<thead>
<tr>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory-guided</td>
<td>A subtype of volitional saccades generated to the remembered location of a previously displayed visual target when the target is no longer visible.</td>
</tr>
<tr>
<td>Antisaccades</td>
<td>A subtype of volitional saccade generated intentionally in the direction opposite to a visual target. Require not only intentional generation of a saccade in the opposite direction, but also suppression of a saccade to the visual target.</td>
</tr>
<tr>
<td>Self-paced</td>
<td>Volitional saccades made between two continuously present targets without verbal commands.</td>
</tr>
<tr>
<td>Reflexive</td>
<td>Saccades involuntarily generated to an unexpected novel visual target, such as to an object unexpectedly appearing in the peripheral vision.</td>
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</tbody>
</table>
Extensive cortical and subcortical networks are involved in the planning and execution of saccades, including the frontal eye fields (FEF), the dorsolateral prefrontal cortex (DLPFC), the supplementary motor area (SMA), and the cingulate eye fields (CEF). The diffuse nature and complexity of this network render it susceptible to injury in mild TBI. Frontal and antero-temporal brain regions are the most common sites of focal lesions after closed head injury. When MRI fails to disclose pathology, functional assessment of frontal cortex may be sought with exploration of saccades paradigms heavily indicative of frontal function, such as memory-guided saccades and antisaccades. However, the complexity of this network and how each structure controls each saccade parameter is complex. Localization of a saccadic abnormality to a specific neuronal population may be challenging. Table 2 outlines a simplified schema of the role played by individual structures in generation of specific saccade types. The results of published studies of saccades in adults with mild TBI are summarized in Table 3.

### Table 2. Simplified schema of the role of cortical structures in saccade subtype deficits

<table>
<thead>
<tr>
<th>Saccade Type</th>
<th>Structures Involved</th>
<th>Deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory-guided saccades</td>
<td>FEF, DLPFC, PPC</td>
<td>Reduced accuracy and increased response errors. Lesions in SMA cause errors in sequences of memory-guided saccades.</td>
</tr>
<tr>
<td>Antisaccades</td>
<td>FEF triggers correct antisaccade. DLPFC inhibits reflexive misdirected saccades.</td>
<td></td>
</tr>
<tr>
<td>Self-paced saccades</td>
<td>May be due to FEF lesions or lesions in connections between FEF or DLPFC and SC.</td>
<td></td>
</tr>
<tr>
<td>Reflexive visually-guided saccades</td>
<td>Governed by PEF.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: FEF frontal eye fields, DLPFC dorsolateral prefrontal cortex, PPC posterior parietal cortex, SMA supplementary motor area, SC superior colliculus, PEF parietal eye fields.

### Table 3. Saccades in mild TBI (mTBI)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Time since injury</th>
<th>Memory-guided saccades</th>
<th>Antisaccades</th>
<th>Self-paced saccades</th>
<th>Simple reflexive saccades</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000 Crevits</td>
<td>25 mTBI – no alcohol, 6 mTBI – alcohol 27 controls</td>
<td>Within 24 hours</td>
<td>Reduced latencies and errors only in mTBI with alcohol</td>
<td>Reduced latencies and errors only in mTBI with alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002 Heitger</td>
<td>30 mTBI, 30 controls</td>
<td>Within 9 days</td>
<td>Reduced latencies and errors*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2004 Heitger</td>
<td>28 mTBI, 28 controls</td>
<td>Within 16 days</td>
<td>Errors reduced, accuracy improved</td>
<td>Reduced latencies and errors reduced, accuracy improved</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2006 Heitger</td>
<td>37 mTBI, 37 controls</td>
<td>1 week and 3, 6, 12 months</td>
<td>Improved but ongoing deficits at all intervals</td>
<td>Improved but ongoing deficits at all intervals</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2007 Pearson</td>
<td>12 boxers</td>
<td>Within 12 hours before match, within 7 minutes of match, and days later</td>
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</tbody>
</table>

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*Table 3 Continued*

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<table>
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<tr>
<th>Study</th>
<th>Number of subjects</th>
<th>Time since injury</th>
<th>Memory-guided saccades</th>
<th>Antisaccades</th>
<th>Self-paced saccades</th>
<th>Simple reflexive saccades</th>
</tr>
</thead>
<tbody>
<tr>
<td>2007 Kraus³³</td>
<td>20 mTBI, 19 controls</td>
<td>Mean 65 months</td>
<td>á errors</td>
<td>No difference</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2009 Heitger³⁴</td>
<td>36 PCS, 36 prior mTBI with good recovery</td>
<td>140 days for PCS, 163 days for prior mTBI</td>
<td>Poorer performance in PCS***</td>
<td>Poorer performance in PCS</td>
<td>Poorer performance in PCS</td>
<td>No difference</td>
</tr>
<tr>
<td>2014 and 2015 Johnson⁶⁵,⁶⁶</td>
<td>9 mTBI, 9 controls</td>
<td>Acutely within 7 days and 30 days post-injury</td>
<td>Acutely: á errors, á accuracy</td>
<td>Acutely: á errors, á accuracy</td>
<td>Acutely: Fewer saccades, 30 days: Fewer saccades</td>
<td></td>
</tr>
</tbody>
</table>

PCS = post-concussive syndrome

*Memory-guided saccade sequences with 2-3 steps were tested, rather than single memory-guided saccades

**Possibly different from 2004 Heitger and 2007 Kraus due to inter-subject vs. intra-subject comparisons

***Abnormal saccades of all types were more likely to be present in PCS with higher symptom burden

^In 2014 study, 9 subjects. In 2015 follow up study, 7 subjects. Ocular motor testing was performed simultaneously with fMRI, which showed increased areas of activation in mTBI.

EFFERENT DYSFUNCTION IN MILD TBI: FUTURE PROGRESS

The King-Devick test, a task of rapid number naming, has been well-validated as a sensitive sideline measure for concussion detection.⁶⁷ This test functions as a pseudo-reading task, which broadly captures aspects of afferent visual function, attention, language, visual fixation, and saccadic eye movements. Slowing of the total time to read the three test cards occurs in acute concussion; however the explanation as to why this occurs remains forthcoming. Possibilities include saccadic slowing, increased duration of fixations, increased blinking, increased overall numbers of saccades due to backtracking or inaccurate saccades, excessive saccadic intrusions superimposed upon otherwise normal eye movements, and attentional and cognitive deficits. Future research avenues include bridging the sidelines, the clinic, and the laboratory with assessment of oculomotor behaviour during rapid number naming and with assessments for correlations between laboratory abnormalities of saccades, concussion severity, and recovery.

CME ANSWERS

1. a
2. b Memory-guided saccades are predominantly controlled by the frontal lobes. Express saccades are generated at the level of the superior colliculus. Reflexive saccades are controlled by the parietal lobes.
3. a

REFERENCES


