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Vision-Based Concussion/ Mild Traumatic Brain Injury Diagnostic Tests/ Biomarkers: An Update and Reappraisal

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ABSTRACT

Detection and diagnosis of concussion/mild traumatic brain injury (C/mTBI) has a multitude of general vocational and avocational, as well as public health and educational, implications. A relatively short, focused, updated, high-yield set of subjective and objective clinical vision tests are proposed that we and others have found to be assistive in the process. These vision tests are of a sensory, motor, and/or perceptual nature, many of which are relatively easy to implement in the standard, clinical environment.

Correspondence regarding this article should be emailed to Kenneth J. Ciuffreda, OD, PhD, at kciuffreda@sunyopt.edu. *All statements are the authors' personal opinions and may not reflect the opinions of the College of Optometrists in Vision Development, Vision Development & Rehabilitation or any institution or organization to which the authors may be affiliated. Permission to use reprints of this article must be obtained from the editor.* *VDR is indexed in the Directory of Open Access Journals. Online access is available at covd.org. https://doi.org/10.31707/VDR2019.5.3.p187.*

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INTRODUCTION

For nearly a decade, clinical researchers in our laboratory have had a focus on developing high-yield, vision-based, diagnostic tests/biomarkers for detection of concussion (C)/mild traumatic brain injury (mTBI). These were of either a basic and subjective clinical nature (e.g., near point of convergence)[1,2] or of a more advanced clinical and frequently objective nature (e.g., visual-evoked response).[3] It initially included a large array of potential tests.[4-7] This later culminated in a more focused summary paper in the military literature,[8] especially relevant to the Iraq and Afghanistan wars but also to the sports arena and civilian populations. There was also a very narrowly-focused paper in the clinical optometric literature dealing with vergence dynamics.[9] Both papers dealt solely with objective biomarker diagnostic tests.

The search for one or more such high-yield, vision-based biomarkers is a rapidly evolving area based on the development and testing of new clinical and laboratory approaches/technologies, as well as from our gaining greater understanding and insight into the related visual signs and symptoms, and the underlying neurological control dysfunctions, of this complex and elusive entity. This has lead us, once again, to reconsider and reappraise this area.

We thus propose a focused and relatively short list of both basic clinical and more advanced, objective, high-yield clinical vision tests that should prove helpful for the accurate detection and diagnosis of C/mTBI by the general optometrist and the specialty neuro-optometrist. These proposed tests may also be assistive to others integral to this field, such as the vision therapist, occupational therapist, and sports medicine physician.

Clinical Diagnostic Tests

We, and others, have found the following subjectively-based, clinical tests to reveal

a wide range of abnormal visual response parameters diagnostic for C/mTBI at a high probability level (40-90%). These will be briefly considered below.

The near point of convergence (NPC) (blur/break/recovery) has been well-documented for the detection of C/mTBI.[10-13] The NPC represents the overall, or aggregate, *absolute* maximum response amplitude incorporating the disparity/fusional, accommodative, proximal, and tonic vergence components, all combining in a complex non-linear manner.[2] It is important to measure the NPC from the estimated center-of-rotation of the eyes (i.e., clinically the lateral orbital rim)[2,14] and *not* the forehead.[15] Although the fusional "break" point has been the primary diagnostic parameter used in these studies, from a more functional (and perhaps even diagnostic) viewpoint, the "recovery" value is at least as important. It reflects one's dynamic, refusional ability, once diplopia ensues. The recovery movement should be immediate (i.e., completed in one second) and reflexive in nature, incorporating a large asymmetric vergence response.[16] Neurologically, the break point likely reflects the saturated "step" component of the overall, combined *mini*pulse-step vergence controller signal;[9] the fusional recovery primarily reflects the rapid, dynamic, minipulse aspect alone; and the related step once again for subsequent binocular maintenance. Any "fatigue" effects found with NPC repetition, such as progressive regression and/or slowed dynamic recovery, suggest abnormality of the step and pulse aspects, respectively. Lastly, any symptoms such as headaches, asthenopia, dizziness, etc., caused by this test should be noted.

Vergence facility represents a dynamic, "provocative" test.[2] As conventionally performed at both distance (4pdBO/2pdBI)[17] and at near (12pdBO)/3pdBI),[10] this involves *relative* convergence and divergence. It is purely a dynamic test effectively driven by the vergence minipulse neural component alone. Sustained vergence involving the step component is neither demanded nor desired. This test can be conceptualized as a vergence "stress" test due to its rapid response demand over a short, specified time period (i.e., one minute).[2] Any rate reduction with repetition to assess fatigue effects likely represents an inability to rapidly reconfigure the bidirectional, minipulse component.

Developmental Eye Movement Test (DEM)/ King-Devick Test (K-D) represent two well-documented tests for all three possible injury phases, especially the acute[12] and chronic[18] ones. These tests involve the versional, or conjugate, eye movement system,[16] in particular the rapid saccadic aspect and the intervening fixational pauses. The task is to read aloud the test letters sequentially in a rapid, accurate manner. The neurological controller signal is a *large pulse*-step. The large pulse controls the rapid, dynamic saccadic movement itself, while the step aspect maintains the eyes in the new gaze position. This test reflects the neural integrity of the saccadic "gain" (i.e., the ratio of the initial saccadic amplitude to the intended target amplitude; a gain of 1.0 is optimal). Another aspect that these tests also reflect and assess is one's saccadic sequencing ability.[19] The two aspects are likely interactive. The C/mTBI patient does not exhibit dynamically slowed saccades, but rather inaccurate saccades.[19] They typically execute more saccades than optimally required, thus resulting in longer completion times and increased error rates on these two tests.

Visual motion sensitivity (VMS) test represents another "provocative" test, especially in those patients with either the symptom or suspicion of susceptibility to global, external visual motion.[20-22] This test creates relatively controlled visual motion, especially in the peripheral visual fields, to simulate Gibsonian optic flow.[21] Such external motion can be generated using an OKN drum or tape, or simply the examiner's hands.[21] One needs to fill much of the patient's visual field to assure a maximal effect. The goal is to generate

external visual motion, and not to elicit an OKN motor response per se. The patient with VMS responds immediately, and frequently strongly: they may tightly close their eyes, feel unsteady, jerk their head back, and even demand cessation of the testing. While visual motion processing per se involves cortical areas V5/middle temporal (MT) and medial superior temporal (MST), in real-life conditions, newly-discovered cortical areas V6/6a are also involved.[21] They act to disambiguate one's self-generated motion from visual object/field motion. The second author has developed a detailed protocol with VMS quantification using this OKN drum approach, which will be the subject of a future report.

Binasal occlusion (BNO) can also be used to assess visual motion sensitivity in that subset of C/mTBI patients reporting symptoms of VMS (e.g., balance difficulty in a crowded environment).[3,21,24] Here the patient is typically requested to walk normally down the center of a long hallway, first without and then with the BNO, and compare conditions. If the BNO is effective, then the immediate response might be more ease and confidence ambulating, reduced balance unsteadiness, better direc—tional centering, faster ambulation, and overall reduced VMS symptoms. BNO reduces retinal-image motion in the contralateral, bitemporal hemi-retinas, so it likely affects the areas of visual motion processing as described earlier.

Accommodative facility assessment rep-resents a binocular, "provocative' test of relatively high yield in pre-presbyopic individ-uals with C/mTBI.[2] As performed at near (+/-2D ages 29 years and below; +/-1.50D 30-39 years of age), it involves timed (1 minute), rapid changes in *relative* accommodation. It is purely a dynamic test effectively driven by the accommodative pulse component alone,[25] assuming neurological controller signals similar to the vergence system, as described earlier.[9] Sustained accommodation involving the step component is neither demanded nor desired. This test can be conceptualized as an accommodative "stress" test.[2]

End-point nystagmus assessment repre-sents another test of the versional (i.e., fixational) eye movement system.[16,26] It is elicited at or near one's gaze limit (~60-70 degs.) in normal individuals. In contrast, in the C/mTBI population, we have found it to occur at a much reduced gaze angle (~40-45 degs.) in approximately 50% of the cases. In addition, its response amplitude is noticeably larger than in normals, perhaps reflecting rapid decay of the saccadic step component,[16] and at times with the report of discomfort/pain, especially in upper-left gaze. Further testing is required for confirmation, refinement, and objective quantification (e.g., calibrated video recordings).

Advanced Objective Diagnostic Tests

We, and others, have found the following objectively-based clinical tests to reveal a wide range of abnormal visual system response parameters diagnostic for C/mTBI at a very high probability level (80%-100%). These will be briefly considered below.

Convergence peak velocity has been a test parameter with the highest yield, namely 100% in our laboratory.[9,10,27] This parameter was consistently and significantly reduced by as much 50%, as compared to matched normals. This reflects reduction in the minipulse component.[9] Recently, we have proposed that a simple vergence test stimulus could be integrated into commercially-available eye movement systems (e.g., Right Eye) or into three-dimensional, virtual reality systems (e.g., Oculus) for rapid assessment of this and related diagnostic vergence parameters/biomarkers for C/mTBI.[9] We can even envision a portable, hand-held test device that could be used in a wide range of settings, such as a hospital emergency room, sports sidelines, or even the military theater, with its one minute test time and automated analysis.

Accommodative peak velocity is another oculomotor parameter of equally high-yield (100%) in our laboratory.[28,29] This reflects reduction in the presumed minipulse component.[9,29] It too revealed consistent, markedly reduced (up to 50%) values in this population. Unfortunately, it remains an advanced, clinical test. However, again we can envision a portable, hand-held system integrated into a Badal optical system for compactness, with use in a range of settings, as described earlier.

Pupillary light reflex peak velocity for constriction and dilation are high yield (>90%) tests, which have been found to be consistently and significantly reduced in the chronic C/mTBI population by us[30,31] and others.[32] This too likely reflects reduction in the presumed pulse controller component.[9] Fortunately, a portable, hand-held device is commercially available for clinic use.[30,32] It involves a simple, 5-second test with high-fidelity recordings and automated analysis. Lastly, we are excited about the development of an iPhone app for dynamic pupillometry, and await further test results and validation (www.brightlamp.org).

Visual-evoked response (VEP) with binasal occlusion has been found by us,[3,21] and others,[24] to show an increased response amplitude in that subset of C/mTBI patients with VMS. The yield was from 80%-100%. In contrast, normals showed a consistent **decrease** in this parameter value, which improved the differential diagnosis. The underlying neurology here remains elusive, but likely involves inhibitory and excitatory cortical processes.[3]

Visual-evoked response with neutral density (ND) filters has been another high-yield (>80%) VEP test in this population.[33] While the response latency increases with added ND filters in both the C/mTBI and visually-normal groups, the response increases much more precipitiously in the former group, especially with ND filters of 2.0 and 2.5. Luminance reduction with ND filters effectively delays the neurophysiological response and reduces the neural firing rate.[34] This test is worthy of further evaluation in the C/mTBI population.

DISCUSSION

We have proposed a distilled set of subjective and objective clinical vision tests and related parameters that have been found to be "high-yield, targeted" in the detection and diagnosis of C/mTBI by us and others. The clinical tests have yields of 40-90% (mean ~50%), while the objective tests are even better, with yields from 80-100% (mean ~90%). All, or only some, of the proposed tests are suggested to be used by the clinician for this purpose. Furthermore, it does not preclude the clinician from using what they have found to be "high yield" under their own test conditions and personal experience, or from developing additional tests in the future. The detection and diagnosis of C/mTBI will continue to be an evolving area as technology advances and as we gain greater insight into the vision problems they experience, for example with new brain imaging studies, resulting in better patient care and earlier interventions.[35]

The present findings have a wide range of important societal implications.[36,37] First, there is the question of health care economics. C/mTBI is estimated to cost the United States 75 billion dollars annually,[36,37] and considerably more worldwide with a conservative estimate of 10 million affected people.[36,37] Better and earlier diagnosis, and subsequent visual and other (e.g., physical therapy) interventions, will likely result in more individuals returning-to-work (RTW),[38] thus producing less economic hardship both for the patient as well as the national/world economy. In addition, earlier RTW will enhance the patient's self-esteem, as they would now once again be perceived by themselves and others as being a contributing member of society.[39] Second, there is a major educational impact. That is, when does the student with C/mTBI return-to-learn?[40] Again, better and earlier diagnosis, and therapeutic

interventions, will provide a safer timeline for rejoining their class, perhaps initially with temporary classroom accommodations. Third, use of our suggested testing would assist in the timeline for return-to-duty (RTD).[41] The military would not want a warrior with slowed cognitive abilities, blurred vision, and impaired visual memory in the battlefield. Lastly, it would prove valuable in the detection of acute concussion, for example in the sports domain on the sidelines, for determining presence of a concussion and one's return-to-play (RTP) expectation.[42] Earlier detection and careful subsequent monitoring is imperative, especially to prevent the occurrence of a second concussion before the first has fully resolved, which would compound the problem and delay brain healing.

There are at least three possible future directions. First, studies should be conducted to distill even further the *minimum* number of clinical tests and related parameters that result in the highest diagnostic yield using more advanced/sophisticated analyses, such as an ROC (receiver operator characteristics)[43] approach to obtain the optimal sensitivity and specificity. Thus, perhaps only 2 or 3 of the suggested test parameters might be sufficient to produce a high ROC value (e.g., 0.90 or more), with additional tests thus having a negligible effect.[12] This is especially important for RTL, RTP, RTW, and RTD as discussed earlier. And, if one were forced to pick a *single*, high-yield, objective diagnostic parameter, it would be convergence peak velocity.[9] Second, clinicians and others in the field need to develop new, rapid, non-invasive, and preferably objective tests for the diagnosis and detection of C/mTBI, as well as its possible subsets (e.g., mTBI with VMS). Third, and related to the above, improved diagnostic capability, especially for its subsets, may be important to tailor more focused and specific visual interventions for more rapid and efficacious vocational and avocational outcomes.

Table 1: Basic Subjective Clinical Tests

- Near point of convergence
- Vergence facility
- Developmental Eye Movement Test/King-Devick Test
- End point nystagmus
- Accommodative facility
- Visual motion sensitivity
- Binasal occlusion

Table 2: Advanced Objective Clinical Tests

- Convergence peak velocity
- Accommodative peak velocity
- Pupillary light reflex velocity
- Visual-evoked response amplitude with binasal occlusion
- Visual-evoked response latency with neutral density filter

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