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Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury (mTBI) - a prospective, controlled observational study

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Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury (mTBI) – a prospective, controlled observational study

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ABSTRACT

Objectives: to assess 1) whether objectively measurable visual disturbances are observed more often in patients with mTBI compared to controls and if these disturbances change over time, and 2) whether self-reported visual symptoms after mTBI correlate with objectively detectable changes in visuomotor performance.

Design: A prospective, controlled observational study.

Setting: Emergency department of a general hospital in Stockholm, Sweden.

Participants: Fifteen patients with mTBI, 15 patients with minor musculoskeletal injury but no head trauma and 15 non-injured controls, all aged 18-40 years.

Outcome measures: Symptom assessment using Convergence Insufficiency Symptoms Survey (CISS) and Rivermead Post-concussion Symptoms Questionnaire (RPQ). Visual examination included assessment of visual acuity, accommodation, eye alignment and saccades. Assessments were performed at two time points – baseline (7-10 days) and follow up (75-100 days) after injury.

Results: Near point of convergence (NPC) in mTBI group was receded at baseline and improved significantly at follow up ($p = 0.015$). A significant difference was found between the mTBI group and non-injured controls in accommodative amplitude at baseline ($p = 0.001$). Six out of 13 mTBI patients still had accommodative insufficiency at follow up. At baseline, mTBI patients reported significantly more symptoms according to CISS compared to orthopaedic controls ($p = 0.012$) and non-injured controls ($p = 0.02$). For mTBI patients the CISS score correlated with fusional vergence. No significant difference was found between the groups regarding pro-saccades, anti-saccades and self-paced saccades at any time point.

Conclusion: There are some transient measurable visual changes regarding convergence in mTBI patients during the subacute period after the injury. Our findings of remaining accommodative insufficiency in a considerable proportion of mTBI patients suggest that this visual function should not be overlooked in clinical assessment.

Key words: neurology, mild traumatic brain injury, visual dysfunction, near point of convergence, accommodation, posttraumatic symptoms.

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ARTICLE SUMMARY

Strengths and limitations of this study

- Prospective longitudinal design with measurement at two time points.
- Strict inclusion criteria for mTBI according to American Congress of Rehabilitation Medicine.
- Inclusion of both an uninjured control group and also a group with minor non-head trauma to control for non-specific effects of injury such as pain and distress.
- Study methods include several easily replicable objective optometric measurements.
- The limitation of this study is a small sample of patients with mTBI aged 18-40 years, which limits the generalisability.

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INTRODUCTION

Monitoring recovery after mild traumatic brain injury (mTBI) is mostly based on reported symptoms. Outcome assessment, if this relies on symptoms, might be affected by biopsychosocial factors that might hamper recovery and sustain complaints. There is a need for objective methods to assess and monitor recovery after mTBI as a base for developing evidence based clinical follow up guidelines for patients sustaining mTBI. Oculomotor changes affecting accommodation, eye alignment and eye movements have been highlighted recently as a possible objective correlate of mTBI-related symptoms.

Visual networks are widely spread throughout the brain including cortical and subcortical areas, and several cranial nerves have a role in vision.(1) Traumatic impact to the head, as in mTBI, affects these networks(1, 2) and may result in visual disturbances. Vision is one of the most important senses and as such even a mild impairment may interfere with daily activities. Specific visual symptoms such as blurred vision and double vision are reported only with low frequency in some studies of mTBI.(3, 4) However, there are other complaints experienced by injured individuals, e.g. reading problems, dizziness in visually crowded environments, and issues with near work, where visual disturbance could act as an aggravating factor. Ability to appropriately alter focus, align the eyes and make gaze changes, can be measured objectively, and have been the focus of several recent studies of mTBI.(5-8) Convergence, that is the ability to move both eyes inwards to maintain a single retinal image of objects at different viewing distances,(9) is one of the most frequently described changes in oculomotor measurements after head injury.(10) Symptoms after mTBI, both direct visual symptoms (double vision, blurred vision), and indirect symptoms (increased effort at near work), might be attributed to impaired convergence. Convergence insufficiency (CI) was found in 42-48% of mTBI patients in retrospective studies,(11, 12) and controlled studies of military personnel who have suffered blast-induced mTBI have shown a significant difference in near point of convergence (NPC).(12, 13)

Fusional vergence maintains eye alignment and thereby provides for clear single vision. Impaired fusional vergence causes unstable binocular vision, which may present as losing one's place when reading, blurred or even double vision. Fusion vergence disorders may occur in about 3-6% of an otherwise healthy population with

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vision based symptoms(14, 15) but may be significantly more frequent in TBI patients.(16)

Accommodation provides a clear optical image of an object at different distances through the altering of refractive power in the crystalline lens. Symptoms of accommodative disorders include blurred vision and impaired flexibility to alter focus between near and far. A physiological deterioration of accommodative ability, presbyopia, is to be expected with age. The current study therefore included pre-presbyopic subjects of age 40 or younger. In an otherwise healthy pre-presbyopic population, accommodative changes may be present in up to about 10 % of individuals with vision complaints.(15, 17) Significantly more prevalent accommodative disorders have been found in mTBI patients in the sub-acute stage(13) and also as part of persisting issues.(18, 19)

Saccades are group of rapid eye movements that shift the gaze to areas of interest in the visual field. They are necessary because only a small part of the central retina is capable of high resolution vision. Through purposeful and accurate saccades, initiated without delay, the environment can be scanned and the functional visual field is increased. Thus, an efficient saccade performance is an important base for efficient and safe interactions with the environment and for detailed work such as reading.(20) The initiation and programming of saccades involves cognitive functions that are subserved by complex neuronal networks involving different parts of the brain. Various parameters of saccades have been shown to be affected after mTBI such as latency and accuracy.(21-24)

A recent systematic review of oculomotor-based vision assessment to monitor changes after mTBI found promising, yet preliminary evidence.(25) It was concluded that measurement of oculomotor functions appear useful in detecting changes after mTBI but the strength of evidence in currently available research is not yet sufficient enough to inform clinical guidelines. Some of the limitations addressed were lack of well-defined study populations, description of baseline data and detailed study protocols. Prospective studies with early assessment and follow up of vision related oculomotor changes after mTBI are scarce.(21, 24) In this study we aim to assess oculomotor and visual changes after mTBI prospectively, and compare these to a control group unexposed to head injury but with minor musculoskeletal injury, and a

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non-injured control group. The study objectives are to assess: 1) whether objectively measurable visual disturbances are observed more often in mTBI patients compared to controls and if these disturbances change over time, and 2) whether self-reported visual symptoms after mTBI correlate with objectively detectable changes in visuomotor performance.

METHODS

This work is a part of a prospective controlled observational study on mTBI. The setting was a large emergency department of a general hospital serving the north-east of Stockholm. Fifteen patients with mTBI and a control group of 15 patients with minor trauma to extremities with no head trauma and not requiring surgical intervention were included in to the study between January 2015 and April 2016. A second control group without any traumatic injury included staff from Department of Rehabilitation Medicine, their friends and family members. All study participants were 18-40 years of age. Groups were matched for age. For demographic information see table 1.

The mTBI patients met criteria described in the guidelines of Mild Traumatic Brain Injury Committee of American Congress of Rehabilitation Medicine (ACRM):(26) acute brain injury resulting from mechanical energy to the head from external physical forces: (i) 1 or more of the following: confusion or disorientation, loss of consciousness (LOC) for 30 minutes or less, post-traumatic amnesia (PTA) for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale (GCS)(27) score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of mTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury.

Exclusion criteria

The following patients were excluded: patients with traumatic brain injury and GCS <13, those in need of neurosurgery, previous moderate or severe traumatic brain injury, any head injury in the previous year requiring medical attention, contraindications for MRI, progressive neurological disease or other medical

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conditions with expected short survival, severe visual impairment or manifest strabismus, need for personal help in activities of daily living before the current injury, intoxication with alcohol at the time of the injury, not fluent in Swedish.

Table 1 Demographic data

	mTBI patients	Orthopaedic controls	Non-injured controls
Age, median (range)	25.0.(18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (ER)	14	N/A	N/A
GCS 14 (ER)	1	N/A	N/A
Type of trauma: n (%)	Fall: 7 (47 %) Bicycle: 2 (13 %) Horse back riding: 2 (13 %) Other: 4 (27 %)	Sports: 9 (60 %) Other: 6 (40 %)	

N/A – not applicable

Inclusion procedure

Patients attending the Emergency Department (ED) at Danderyd hospital with mTBI or minor musculoskeletal injury but no head trauma who fulfilled inclusion and exclusion criteria were recruited at ED or if discharged contacted by phone within 1-3 days after the injury. Study participants received written information about the study and gave informed consent.

Data collection

All data related to the injury, GCS on arrival at the ED, results of CT-scan were collected from the medical records. Demographic data were collected by interview at the baseline examination.

All study participants were assessed twice: at baseline, in the subacute phase, (trauma patients 7-10 days after the trauma), and at follow up - 75-100 days after first assessment. Neuropsychological testing and visual assessment were performed at different time points on the same day or on adjacent days.

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Assessments

The mTBI and patients with minor musculoskeletal injury underwent examination with structural magnetic resonance imaging (MRI) and resting state functional magnetic resonance imaging (rsfMRI) of the brain at baseline and at follow up (imaging results will be presented separately). At baseline and follow up all study participants self-rated their symptoms using Rivermead Post-concussion Symptoms Questionnaire (RPQ)(28) and Convergence Insufficiency Symptom Survey (CISS).(29, 30) The RPQ is based on a Likert scale and includes 16 items with ratings: 0 ”no symptoms”, 1 “no more of a problem or transient symptoms”, 2-4 “mild to severe” symptoms. A total sum of all symptom scores (“mild to severe”, excluding ratings of 1) is calculated, max 64. Three or more symptoms after mTBI describes “postconcussional syndrome” in the International Classification of Diseases (ICD-10).(31) The CISS is a valid and reliable instrument,(29) which evaluates near work related visual symptoms. It includes assessment of direct symptoms, such as blur and double vision, as well as indirect symptoms e.g. difficulty maintaining concentration, sleepiness while reading, headache and ocular discomfort. The survey includes 15 questions with ratings from 0 “never” to 4 “always” for assessment of visual symptoms. The total score is 60 and the cut-off score for abnormal levels of symptoms is 21 (this value giving good sensitivity (97,8 %) and specificity (87 %) in otherwise healthy young adults who have presented to optometrists with visual symptoms).(30)

The visual examination was performed by qualified optometrists using standard optometric clinical methods. It included assessment of visual acuity at far and near, refractive error, stereo acuity, near point of accommodation, facility (flexibility) of accommodation, near point of convergence with an accommodative target, non-strabismic eye-turn (heterophoria), eye motility and fusional vergence. Diagnosis of visual dysfunctions were based on established diagnostic criteria(32). The expected accommodative amplitude was defined according to the Hofstetter formula (18.5-1/3 age).(32) Diagnosis of accommodative insufficiency required amplitude less than minimum expected according to the Hofstetter formula (15-1/4 age). Diagnosis of convergence insufficiency required near point of convergence ≥ 6 cm plus at least one of the following; reduced positive fusional vergence at near (< 20 prism diopters) or divergent heterophoria at least four prism diopters greater at near than at distance.(32)

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Saccadic eye movements were recorded using an eye tracker (Tobii TX300, Tobii Corp., Stockholm, Sweden, www.tobii.com). The participant was positioned 60 cm directly in front of the eye tracker display. Three test paradigms were applied to test (1) visually induced pro-saccades; mean latency and gain, (2) self-paced saccades; number of saccades performed in 30 seconds and mean intersaccadic interval (ms), (3) anti-saccades, latency and proportion of erroneous saccades. The stimuli consisted of a dot, diameter 5 mm. In the pro-saccade paradigm the participant fixated a centered cross and then re-fixated to a dot that appeared at 2, 4, 6, or 8 degrees to the left or right of the cross. In the self-paced saccade paradigm two dots were simultaneously presented for 30 seconds at 8 degrees to the left and right of center. The participant was instructed to move the gaze rapidly, as many times as possible, between the dots. In the anti-saccade paradigm the participant viewed a centered cross and then rapidly looked in the opposite direction to that of a dot presented 8 degrees to the left or right of the centre.

Data analyses

All data were analysed using SPSS 23. Due to the relatively small sample size and skewed distribution of data, the nonparametric Kruskal-Wallis (three groups), Mann-Whitney U (two groups), Wilcoxon sign rank tests and Spearman's rank correlation were used for comparison between patients and controls. Two-tailed p-values were used with a critical significance level of $p < 0.05$. Parametric statistics were used for oculomotor measures.

Statistical power calculation: With an expected incidence of visual disturbances in 70 % of mTBI group and 10 % in the control group, 10 individuals per group were needed to detect visual disturbances(10) with 80 % power at alpha 0.05. With an expected drop out rate of 30 %, 15 persons were included in each group.

All participants also rated anxiety, depression and fatigue using Hospital Anxiety and Depression Scale (HADS)(33) and Fatigue Severity Scale (FSS)(34) and underwent neuropsychological testing. These data will be reported separately.

RESULTS

A total of 15 mTBI patients, 15 patients with minor musculoskeletal injuries unexposed to head injury (orthopaedic controls) and 15 non-injured controls were included in the study (table 1). One mTBI patient was excluded due to not completing

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the assessments and two controls were excluded due to manifest strabismus. Two mTBI patients had pathological findings on computer tomography brain: one had a small subdural haemorrhage and the other one a small subarachnoid haemorrhage. Neither required surgery. The median time between injury and baseline assessment was 6.0 days (range 4-12 days) for mTBI, and 8.0 days, range (2-9 days) for orthopaedic controls. The median time between baseline and follow up was 95 days (range 81-225) for mTBI, and 108 days (range 87-324) for orthopaedic controls. No significant difference was found between mTBI and orthopaedic control group regarding time between the injury and assessments (baseline and follow up). Among the consecutive patients who were invited to participate in the study a total of ninety-nine declined; 17 mTBI and 82 orthopaedic controls. Of those who declined, 88 % of mTBI patients and 64 % of minor trauma patients were men, and there was no difference regarding age between participating and non-participating individuals. The reasons stated for not participating were lack of time and inconvenience.
Two individuals in mTBI group and two individuals in orthopaedic control group were lost to follow up despite several reminding phone calls and letters. One person in orthopaedic group did not complete the visual examination.

Symptoms measured by RPQ

There was a significantly higher sum of symptom scores at baseline according to RPQ in mTBI group compared to orthopaedic controls ($p = 0.002$) and to non-inured controls ($p = 0.0005$). Significant difference was found in sum of symptom scores at follow up between mTBI group and orthopaedic controls ($p = 0.003$) and between mTBI group and non-injured controls ($p = 0.0005$) (Mann-Whitney U test). No difference was found between control groups at any time. Sum of symptom scores decreased in mTBI group over time but the difference did not reach statistical significance ($p = 0.092$) (Wilcoxon signed rank test).

There was a significant difference regarding number of symptoms in RPQ (rated 2-4, “minor to severe”) between mTBI group and orthopaedic control group at baseline ($p = 0.003$), and at follow up ($p = 0.0005$), and between mTBI group and non-injured control group at baseline ($p = 0.002$) and at follow up ($p = 0.0004$).

Visual examination

No cranial nerve palsies or direct trauma related pathology were found. Insufficient accommodation (AI) and convergence (CI) were identified. At baseline three mTBI

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patients had combined CI/AI and nine had AI. At follow up one mTBI patient still had CI and six had AI. Five orthopaedic controls had AI at baseline and six at follow up. Two non-injured controls with CI and two with AI were found at baseline and at follow up.

The near point of convergence (NPC) changed significantly in the mTBI group between the baseline and follow up ($p = 0.015$) (figure 1). There was no significant difference in NPC between mTBI group and each of the control groups at any time.

(Insert Figure 1 here)

Figure 1 Near point of convergence in mTBI group at baseline and at follow up measured in cm. The lower the value, the better convergence performance. The box indicates median, upper and lower quartile. The whiskers indicate min and max excluding outliers. The x's indicate outliers and miniature squares indicate mean values.

A significant difference was found at baseline in the magnitude of deviation from expected accommodative amplitude in mTBI group compare to non-injured controls ($p = 0.001$) (figure 2). At follow up six out of 13 mTBI patients still presented with reduced accommodative amplitude which met diagnostic criteria for accommodative insufficiency.

Performance in accommodative facility in mTBI group improved marginally from baseline to follow up but this did not reach statistical significance.

(Insert Figure 2 here)

Figure 2 Deviation from expected accommodative amplitude. The higher the negative value, the greater the deviation (insufficiency). Closer to zero is better. The box indicates median, upper and lower quartile. The whiskers indicate min and max excluding outliers. The x's indicate outliers and miniature squares indicate mean values.

The analysis of fusional vergences did not show any significant differences at the group level. At baseline, reduced positive fusional vergences (< 20 prism diopters) at near point of focus were found in four mTBI patients, four orthopaedic controls and marginally reduced in two non-injured controls.

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Saccade performance

In the pro-saccade task no significant differences in latency or gain were found between the groups or test occasions. That is, performance in terms of reaction time and accuracy was not different at the group level. One mTBI patient and one non-injured control exhibited a markedly prolonged latency both at baseline and follow up.

In the self-paced saccade task the mTBI group performed slightly fewer saccades on average at both baseline and follow up compared to controls but the difference was not statistically significant. The mTBI group also showed a slightly elevated intersaccadic interval at baseline but this was not statistically significant.

In the anti-saccade task all groups performed equally well at both test occasions with no statistically significant differences in latency or proportion of erroneous saccades. The mTBI group showed an apparent greater variability in latency with three subjects exhibiting prolonged latency.

Assessment of visual symptoms

Patients with mTBI had more visual symptoms with near work compared to the two control groups as measured by the CISS score at baseline: mTBI vs. orthopaedic controls ($p = 0.012$) and mTBI vs. non-injured controls ($p = 0.02$) (Mann-Whitney U test). The median value of CISS score in mTBI group at baseline was 24. It then decreased to 19 at follow up but the change did not reach statistical significance. The CISS score was below cut-off level at both time points in control groups. A CISS score of 21 or higher was applied as the cut-off for abnormal visual symptoms. The association with convergence and/or accommodative insufficiency was analysed (table 2). No significant associations between symptoms and objective findings were found using the Fisher's exact test. At baseline nine out of 12 mTBI patients with a vision diagnosis were identified using CISS. Of these 12 patients five had scored two or higher on one or both of the RPQ items concerning blurred or double vision. At follow up seven mTBI patients still had a vision diagnosis; one with convergence- and six with accommodative insufficiency. Three of these patients scored as symptomatic on CISS. Three of these patients also scored two or greater on RPQ items concerning blurred or double vision however there was only an overlap for two patients.

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Table 2 Vision diagnoses (accommodative– and/or convergence insufficiency) versus CISS symptom score.

Subjects	Examination	Vision diagnosis	CISS < 21	CISS ≥ 21	Score ≥ 2 on RPQ blurred or double vision
mTBI patients	Baseline	No diagnosis	2	1	-
	n=15	Diagnosis	3	9	5
	Follow up	No diagnosis	4	2	1
	n=13	Diagnosis	4	3	3
Orthopaedic controls	Baseline	No diagnosis	8	1	-
	n=14	Diagnosis	5	-	-
	Follow up	No diagnosis	5	1	-
	n=12	Diagnosis	6	-	-
Non-injured controls	Baseline	No diagnosis	11	-	1
	n=15	Diagnosis	4	-	1
	Follow up	No diagnosis	10	1	-
	n=15	Diagnosis	3	1	-

In mTBI group CISS score at baseline correlated with reduced positive fusional vergence measured at near, i.e. the capacity to maintain clear single vision while performing near work ($r = -0.6$; $p = 0.02$) (figure 3).

(Insert Figure 3 here)

Figure 3 CISS score versus positive fusional vergence in mTBI patients. Higher positive fusion value corresponds to better function.

DISCUSSION

We have found transient objectively measured visual disturbances in a well-defined mTBI group. We also observed differences in visual measurements between mTBI group and two control groups.

As expected, mTBI patients reported significantly more symptoms on the RPQ compared to controls at baseline. Symptoms after mTBI, such as fatigue, headache and cognitive problems are not specific to the head injury, and therefore referred to as posttraumatic symptoms as it was concluded in the systematic review on prognosis after mTBI.(35) Previous studies have demonstrated that similar symptoms are

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present after any trauma because of emotional distress and pain related to the injury.(36) However, patients with mTBI report more symptoms then individuals without injury to the head.(37)

We found a significant change in NPC in the mTBI group between the baseline and follow up. Receded NPC has previously been suggested as a potential sensitive vision based biomarker after mTBI(8) and our findings support this. Similar findings in NPC performance were made by Capo-Aponte and co-workers when comparing mTBI patients and controls.(13) However, the median NPC at baseline was within 10 cm, which may be clinically considered as within the tolerance limit,(9) and therefore not pose a clinical sign for further examination regarding suspected convergence insufficiency. On the other hand, according to established diagnostic criteria for convergence insufficiency, any NPC greater than six cm is considered insufficient.(32)

The mechanism behind the spontaneous recovery of NPC in the present patient sample remains to be understood. The convergence responses are based on visual processing of binocular disparity and correct ocular motor alignment trough vergence eye movements. Given the recovery of NPC any manifest structural injury affecting motor function (vergence eye movements) can probably be ruled out. Some of the remaining aspects to consider are the sensory-motor integration and the ability to respond appropriately to the stimulus. Certain tasks, including the actual test condition for NPC, means that the subject must exert maximal convergence effort to maintain single vision of a very near target. This most likely involves voluntary effort. A question for further discussion is how the constellation of somatic symptoms, cognitive impairments and fatigue, known to be associated with mTBI, may affect the capacity to perform maximally. Our clinical observations during this study, along with previous research, may suggest that these factors can have aggravating effects.(16)

In accordance to previous studies,(13) a significant difference in accommodation between mTBI and each of the control groups at the baseline was found in our study.

The accommodative amplitude was significantly lower in mTBI compared to controls at baseline. It then recovered to a certain degree at follow up but six mTBI patients still presented with deviations meeting the diagnostic criteria for accommodative

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insufficiency. This corresponds to almost half of the mTBI patients (n=13) who were examined at the follow up around three months after the injury. To our knowledge there is quite limited research available regarding the expected course of spontaneous improvement. Capo Aponte et al. found significantly reduced accommodative amplitude 15-45 days after injury.(13) There are some indications that spontaneous recovery may occur up to a year after the injury(32) but also that it may be part of persisting issues even long time after the injury.(18, 19) Mechanisms contributing to slow or incomplete spontaneous recovery of accommodation are unclear. Our findings, along with previous observations,(18) indicate the importance of being aware of possible accommodative disorders and its effects on the patients capacity to perform daily activities.

We found that mTBI patients had significantly more visual symptoms as measured by CISS score than minor trauma- and non-injured controls. CISS score decreased from baseline to follow up without the difference reaching significance. CISS scores never reached the cut-off point 21 in either control groups. Our findings about reporting visual disturbances at near work after mTBI are consistent with previous studies study.(13)

We were not able to replicate the findings of previous studies that found differences in several measures of saccadic eye movements between mTBI patients and controls. An explanation could be that changes in saccadic reaction time/latency are subtle, transient, and possibly only to be demonstrated directly after a minor trauma to the head. In our study, baseline optical examination took place a few days after mTBI.

Our findings are in line with a study of amateur boxers where saccadic latency was expressed as latency distribution and was measured at several time points, with the baseline before the boxing match (pre-fight) and at 3 days, 7 days and 12 days after-fight, after blows to the head.(24) Results in this study showed increased mean saccadic latency distribution directly after the fight, however 12 days later the mean latency had returned to baseline. The small number of participants and lack of the description of mTBI criteria limit interpretation of findings in that study.

The strength of our study is two control groups. Traumatic injury generally can impact on reporting of various symptoms related to acute posttraumatic stress and pain. Therefore, to avoid confounding, we included group of patients with minor

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musculoskeletal injuries without trauma to the head, presenting at the same emergency department.

Study limitations

When the study population is small, there is always a risk for type II error, that is the risk of not revealing a true difference in the studied population. The differences found between mTBI patients and controls regarding oculomotor measures were few and the within group variations were large. The degree of overlap between groups and incomplete correlation between visual symptoms and objective measurements, suggest that caution is appropriate when interpreting findings in an individual patient, based on the current state of knowledge. However several aspects merit further investigation.

Study participants were 18-40 years old making the mTBI patient group in this explorative study highly selected. This age limitation was chosen to minimize the effect of presbyopia on study results. Our findings will have relevance regarding the large number of young adults suffering head trauma, but will not be directly applicable to older patients, which limits the generalisability.

Future recommendations

Larger confirmatory studies are needed to clarify the clinical role the transient visual disturbances observed in this study. The role of vergence and accommodation as potential biomarkers for mTBI and their interplay with persisting symptoms such as fatigue also needs further elucidation.

Furthermore, investigations of visual disturbances after mTBI should aim to determine if visual testing in subacute stage after mTBI could help to predict long lasting symptoms and be a target for intervention to promote recovery.

CONCLUSIONS

Some transient measurable visual changes regarding convergence were noted in mTBI patients during the subacute period after injury. The finding of persistent accommodative insufficiency in a substantial proportion of mTBI patients requires further evaluation; this could be either a biomarker for persistent functional impairment in neural networks, or a target for intervention to promote recovery, or possibly both.

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Contributors: GM and JJ contributed to design of the study, were responsible for data collection, wrote initial draft of manuscript, performed statistical analysis, and contributed to the analysis of results and interpretation of findings. CND, TP, MM were main contributors to study design, contributed to data collection, analysis of results and interpretation of the findings. AKG critically revised manuscript, contributed to data analysis and interpretation. All authors read, commented and approved the final manuscript.

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Competing interests: None declared.

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Ethics approval: Ethics approval was obtained from the Regional ethical review board in Stockholm, diary number 2014/597-31/1.

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Data sharing statement: No additional data are available.

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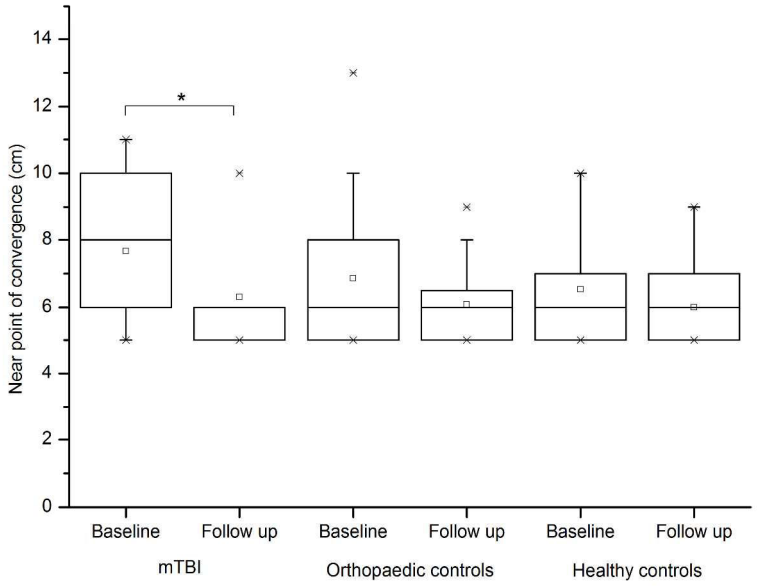

Figure 1 Near point of convergence in mTBI group at baseline and at follow up measured in cm. The lower the value, the better convergence performance. The box indicates median, upper and lower quartile. The whiskers indicate min and max excluding outliers. The x's indicate outliers and miniature squares indicate mean values.

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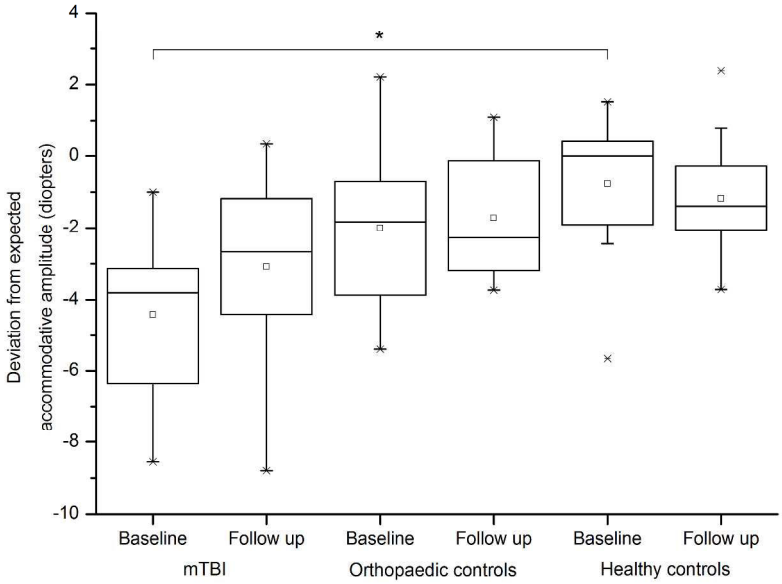

Figure 2 Deviation from expected accommodative amplitude. The higher the negative value, the greater the deviation (insufficiency). Closer to zero is better. The box indicates median, upper and lower quartile. The whiskers indicate min and max excluding outliers. The x's indicate outliers and miniature squares indicate mean values.

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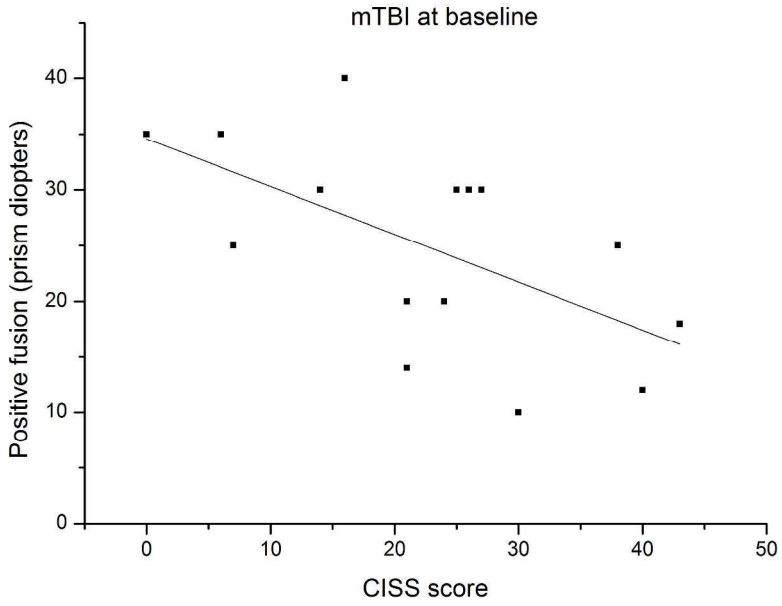

Figure 3 CISS score versus positive fusional vergence in mTBI patients. Higher positive fusion value corresponds to better function.

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Table 1. Demographic data

	mTBI patients	Orthopaedic controls	Non-injured controls
Age, median (range)	25.0.(18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (ER)	14	N/A	N/A
GCS 14 (ER)	1	N/A	N/A
Type of trauma: n (%)	Fall: 7 (47 %) Bicycle: 2 (13 %) Horse back riding: 2 (13 %) Other: 4 (27 %)	Sports: 9 (60 %) Other: 6 (40 %)	

N/A – not applicable

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Table 2. Vision diagnoses (accommodative– and/or convergence insufficiency) versus CISS symptom score.

Subjects	Examination	Vision diagnosis	CISS < 21	CISS ≥ 21	Score ≥ 2 on RPQ blurred or double vision
mTBI patients	Baseline	No diagnosis	2	1	-
	n=15	Diagnosis	3	9	5
	Follow up	No diagnosis	4	2	1
	n=13	Diagnosis	4	3	3
Orthopaedic controls	Baseline	No diagnosis	8	1	-
	n=14	Diagnosis	5	-	-
	Follow up	No diagnosis	5	1	-
	n=12	Diagnosis	6	-	-
Non-injured controls	Baseline	No diagnosis	11	-	1
	n=15	Diagnosis	4	-	1
	Follow up	No diagnosis	10	1	-
	n=15	Diagnosis	3	1	-

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Research checklist

STROBE Statement - checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable	11-13

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		of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.
NA – not applicable

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BMJ Open

Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury (mTBI) - an exploratory Swedish prospective observational study

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	mild traumatic brain injury, visual dysfunction, near point of convergence, accommodation, posttraumatic symptoms, NEUROLOGY

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Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury (mTBI) – an exploratory Swedish prospective observational study

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ABSTRACT

Objectives: To assess 1) whether visual disturbances can be demonstrated with objective measures more often in patients with mild traumatic brain injury (mTBI) compared to controls and if these disturbances change over time, and 2) whether self-reported visual symptoms after mTBI correlate with objectively measurable changes in visuomotor performance.

Design: A prospective, controlled observational study.

Setting: Emergency department of a general hospital in Stockholm, Sweden.

Participants: Fifteen patients with mTBI, 15 patients with minor orthopaedic injury but no head trauma, and 15 non-injured controls, aged 18-40 years.

Outcome measures: Visual examination included assessment of visual acuity, accommodation, eye alignment and saccades. Assessments were performed at two time points – baseline (7-10 days) and follow-up (75-100 days) after injury. Symptom assessment using Convergence Insufficiency Symptoms Survey (CISS) and Rivermead Post-concussion Symptoms Questionnaire.

Results: Near point of convergence in the mTBI group was receded at baseline and improved significantly at follow-up (p=0.015). The accommodative amplitude was significantly lower in the mTBI group compare to non-injured controls at baseline (p =0.001). Six out of 13 mTBI patients who were followed up had accommodative insufficiency. At baseline, mTBI patients reported significantly more symptoms according to CISS compared to orthopaedic controls (p=0.012) and non-injured controls (p=0.02). For mTBI patients the CISS score correlated with fusional vergence. No significant difference was found between the mTBI and control groups regarding pro-saccades, anti-saccades and self-paced saccades at any time point.

Conclusion: There are some transient measurable visual changes regarding convergence in mTBI patients during the subacute period after the injury. Our findings of persistence of accommodative insufficiency in a considerable proportion of mTBI patients suggest that this visual function should not be overlooked in clinical assessment.

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Key words: neurology, mild traumatic brain injury, visual dysfunction, near point of convergence, accommodation, posttraumatic symptoms.

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ARTICLE SUMMARY

Strengths and limitations of this study

- Prospective longitudinal design with measurement at two time points.
- Strict inclusion criteria for mTBI according to American Congress of Rehabilitation Medicine.
- Inclusion of both an uninjured control group and a group with minor orthopaedic injuries without trauma to the head to control for non-specific effects of injury such as pain and distress.
- Study methods include several easily replicable optometric measurements.
- The generalisability of this study is limited because the sample of patients with mTBI was small in size and restricted in age range.

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INTRODUCTION

There is a need for objective methods to assess and monitor recovery after mTBI, as a base for developing evidence based clinical follow-up guidelines. Oculomotor changes affecting accommodation, eye alignment and eye movements have been highlighted recently as a possible measurable correlate of symptoms related to a mild traumatic brain injury.(1-4) A recent systematic review of oculomotor-based vision assessment to monitor changes after mTBI found promising, yet preliminary evidence.(5) It was concluded that measurement of oculomotor functions appeared useful in detecting changes after mTBI, but the strength of evidence in currently available research is not yet sufficient enough to inform clinical guidelines.

Traumatic impact to the head, as in mTBI, may affect visual networks that are widely spread throughout the brain,(1, 6) and thus result in visual disturbances. Visual impairments of different kinds have been found in several studies with prevalence up to 70 percent in a cohort of patients with long lasting problems after mTBI.(4, 7, 8) However, these studies have several limitations such as retrospective design, selection bias, heterogeneity regarding severity of injury, and lack of appropriate control groups. Prospective studies with early assessment and follow- up of vision related oculomotor changes after mTBI are scarce.(9, 10)

Ability to appropriately alter focus, align the eyes and make gaze changes, can be measured, and has been the focus of several recent studies of mTBI.(11-14) Convergence, that is the ability to move both eyes inwards to maintain a single retinal image of objects at different viewing distances,(15) is one of the most frequently described oculomotor measurements where changes after head injury have been reported.(16) Symptoms after mTBI, both direct visual symptoms (double vision, blurred vision), and indirect symptoms (increased effort at near work

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might be attributed to impaired convergence. Recent test protocols using eye tracking have added knowledge about the physiology of convergence eye movements in those mTBI patients with convergence related symptoms.(17) These methods appear promising in that they can provide additional information about subtle changes affecting oculomotor efficiency and subsequent symptoms. Convergence insufficiency (CI) was found in 42-48% of mTBI patients in retrospective studies,(4, 7) and controlled studies of military personnel who have suffered blast-induced mTBI have shown a significant difference in near point of convergence (NPC).(3,7)

Fusional vergence aligns the two eyes and thereby provides for clear single vision. Impaired fusional vergence causes unstable binocular vision, which may present as losing one's place when reading, blurred or even double vision. Fusion vergence disorders may occur in about 3-6% of an otherwise healthy population with vision based symptoms,(18, 19) but may be significantly more frequent in TBI patients.(20)

Accommodation provides a clear optical image of an object at different distances through the altering of refractive power in the crystalline lens. Symptoms of accommodative disorders include blurred vision and impaired flexibility to alter focus between near and far. A physiological deterioration of accommodative ability, presbyopia, is to be expected with age. The current study therefore included pre-presbyopic subjects of age 40 or younger. In an otherwise healthy pre-presbyopic population, accommodative changes may be present in up to about 10 % of individuals with vision complaints.(19, 21) Significantly more prevalent accommodative disorders have been found in mTBI patients in the sub-acute stage,(3) and also as part of persisting issues.(22, 23)

Saccades are a group of rapid eye movements that shift the gaze to areas of interest in the visual field. Through purposeful and accurate saccades, executed in quick succession, the environment can be scanned and functional visual field is increased. Thus, an efficient saccadic performance is an important base for efficient and safe interaction with the environment, and for detailed work such as reading.(24) The initiation and programming of saccades involves cognitive functions that are subserved by complex neuronal networks involving different parts of the brain. Parameters of saccades, such as latency and accuracy, have been shown to be affected after mTBI.(2, 9, 10, 25)

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In this study we aim to assess oculomotor and visual changes after mTBI prospectively, and compare these to a control group unexposed to head injury but with minor orthopaedic injury, and to a non-injured control group. The orthopaedic control group is important to control for non-specific effects of pain and distress after trauma, and allow evaluation of brain injury specific effects.

The study objectives are to assess: 1) whether visual disturbances can be demonstrated with objective measures more often in mTBI patients compared to controls and if these disturbances change over time, and 2) whether self-reported visual symptoms after mTBI correlate with objectively measurable changes in visuomotor performance.

METHODS

This work is a part of a prospective controlled observational study on mTBI. The setting was a large emergency department (ED) of a general hospital serving the north-east of Stockholm. Patients with mTBI and a control group of patients with minor orthopaedic trauma to extremities, but no head trauma and not requiring surgical intervention, were included to the study. A second control group without traumatic injury included staff from Department of Rehabilitation Medicine, their friends and family members. All study participants were 18-40 years of age. Groups were matched for age. For demographic information, see Table 1.

Inclusion was conducted between January 2015 and January 2016, and was stopped when 15 persons were included in each group, in accordance with the power calculation below.

A power calculation was conducted: with an expected incidence of visual disturbances in 70 % in the mTBI group,(4, 7, 8) and 10 % in the control group(19, 21), 10 individuals per group were needed to detect visual disturbances with 80 % power at alpha 0.05. With an expected drop out rate of 30 %, 15 persons would be needed in each group.

The mTBI patients met criteria described in the guidelines of Mild Traumatic Brain Injury Committee of American Congress of Rehabilitation Medicine:(26) acute brain injury resulting from mechanical energy to the head from external physical forces: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30

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minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale (GCS)(27) score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations of mTBI must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury.

Exclusion criteria

The following patients were excluded: patients with traumatic brain injury and GCS <13, those in need of neurosurgery, previous moderate or severe traumatic brain injury, any head injury in the previous year requiring medical attention, contraindications for MRI (magnetic resonance imaging), progressive neurological disease or other medical conditions with expected short survival, severe visual impairment or manifest strabismus, need for personal help in activities of daily living before the current injury, intoxication with alcohol at the time of the injury, not fluent in Swedish.

Table 1 Demographic data

	mTBI patients	Orthopaedic controls	Non-injured controls
Age, median (range)	25.0 (18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (ED)	14	N/A	N/A
GCS 14 (ED)	1	N/A	N/A
Type of trauma: n (%)	Fall: 7 (47 %) Bicycle: 2 (13 %) Horse back riding: 2 (13 %) Other: 4 (27 %)	Sports: 9 (60 %) Other: 6 (40 %)	

N/A – not applicable

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Inclusion procedure

Patients attending the ED at Danderyd hospital with mTBI or with minor orthopaedic injury but no head trauma who fulfilled inclusion and exclusion criteria were recruited at ED or if discharged contacted by phone within 1-3 days after the injury. Study participants received written information about the study and gave informed consent.

Data collection

All data related to the injury, GCS on arrival at the ED, and results of computerised tomography scan (CT-scan), were collected from the medical records. Demographic data were collected by interview at the baseline examination.

All study participants were assessed twice: at baseline, in the subacute phase, (trauma patients 7-10 days after the trauma), and at follow-up - 75-100 days after first assessment. Neuropsychological testing and visual assessment were performed at different time points on the same day or on an adjacent day.

Assessments

The mTBI and patients with minor orthopaedic injury underwent examination with structural MRI and resting state functional MRI of the brain at baseline and at follow-up (imaging results will be presented separately). At baseline and follow-up all study participants self-rated their symptoms using Rivermead Post-concussion Symptoms Questionnaire (RPQ),(28) and Convergence Insufficiency Symptom Survey (CISS).(29, 30) The RPQ is based on a Likert scale and includes 16 items with ratings: 0 ”no symptoms”, 1 “no more of a problem or transient symptoms”, 2-4 “mild to severe” symptoms. A total sum of all symptom scores (“mild to severe”, excluding ratings of 1) is calculated, with a maximum score of 64. Three or more symptoms after mTBI describes “postconcussional syndrome” in the International Classification of Diseases, 10th revision.(31) The CISS is a valid and reliable instrument,(29) which evaluates near work-related visual symptoms. It includes assessment of direct symptoms, such as blur and double vision, as well as indirect symptoms (e.g., difficulty maintaining concentration, sleepiness while reading, headache and ocular discomfort). The survey includes 15 questions with ratings from 0 “never” to 4 “always” for assessment of visual symptoms. The total score is 60 and the cut-off score for abnormal levels of symptoms is 21. This value giving good sensitivity (97.8 %) and specificity (87 %) in otherwise healthy young adults who have presented to optometrists with visual symptoms.(30)

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The visual examination was performed by licensed optometrists, using standard optometric clinical methods. It included assessment of visual acuity at far and near, refractive error, stereo acuity, near point of accommodation, facility (flexibility) of accommodation, near point of convergence with an accommodative target, non-strabismic eye-turn (heterophoria), eye motility and fusional vergence. Diagnosis of visual dysfunctions were based on established diagnostic criteria.(32) NPC was measured using the push-up method (RAF rule). Positive fusional vergence (PFV) was measured with a prism bar. In both cases the patient is instructed to try as hard as possible to maintain single vision and to report when perceiving double vision. Meanwhile, the examiner carefully observes eye alignment in order to verify the patient's response. The expected accommodative amplitude was defined according to the Hofstetter formula (18.5-1/3 age).(32) Diagnosis of accommodative insufficiency (AI) required amplitude less than minimum expected according to the Hofstetter formula (15-1/4 age). Diagnosis of CI required near point of convergence ≥ 6 cm plus at least one of the following; reduced PVF at near (< 20 prism diopters) or divergent heterophoria at least four prism diopters greater at near than at distance.(32) Saccadic eye movements were recorded (spatial res 0.15 degrees; temporal res 300 Hz) using an eye tracker (Tobii TX300, Tobii Corp., Stockholm, Sweden, www.tobii.com). The participant was positioned 60 cm directly in front of the eye tracker display. Three test paradigms were applied to test (1) visually induced pro-saccades; mean latency and gain, 2) anti-saccades; latency of correctly performed saccades and proportion of erroneous saccades, (3) self-paced saccades; number of saccades performed in 30 seconds and mean intersaccadic interval (ms). The stimuli consisted of a dot with a diameter of 5 mm. In the pro-saccade paradigm the participant fixated a centered cross and then re-fixated to a dot that appeared at 2, 4, 6, or 8 degrees to the left or right of the cross. In the anti-saccade paradigm the participant viewed a centered cross and then rapidly looked in the opposite direction to that of a dot presented 8 degrees to the left or right of the centre. In the self-paced saccade paradigm two dots were simultaneously presented for 30 seconds at 8 degrees to the left and right of centre. The participant was instructed to move the gaze rapidly, as many times as possible, between the dots.

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Data analyses

All data were analysed using SPSS 23. Due to the relatively small sample size and skewed distribution of data, the nonparametric Kruskal-Wallis (three groups), Mann-Whitney U (two groups), Wilcoxon sign rank tests and Spearman's rank correlation were used for comparison between patients and controls. Two-tailed p-values were used with a critical significance level of $p < 0.05$. Parametric statistics (a two-way repeated measures ANOVA and t-test) were used for oculomotor measures. Fischer's exact test was applied for analysis of the categorical data and small sample size.

All participants also rated anxiety, depression and fatigue using Hospital Anxiety and Depression Scale (HADS)(33) and Fatigue Severity Scale (FSS),(34) and underwent neuropsychological testing. These data will be reported separately.

RESULTS

A total of 15 mTBI patients, 15 orthopaedic controls, and 15 non-injured controls were included in the study (Table 1). Two of the 15 mTBI patients had pathological findings on CT-scan of the brain: one had a small subdural haemorrhage and the other a small subarachnoid haemorrhage. Neither required surgery. The median time between injury and baseline assessment was 6.0 days (range 4-12 days) for mTBI, and 8.0 days, (range 2-9 days) for orthopaedic controls. In order to minimize dropouts, we extended the planned follow-up time. The median time between baseline and follow-up was 95 days (range 81-225) for mTBI, and 108 days (range 87-324) for orthopaedic controls. No significant difference was found between mTBI subjects and the orthopaedic control group regarding time between the injury and assessments (baseline and follow-up). Among the consecutive patients who were invited to participate in the study a total of ninety-nine declined; 17 mTBI and 82 orthopaedic controls. Of those who declined, 88 % of mTBI patients and 64 % of orthopaedic controls were men, and there was no difference regarding age between participating and non-participating individuals. The reasons stated for not participating were lack of time and inconvenience. Two individuals in the mTBI group and two individuals in the orthopaedic control group were lost to follow-up despite several follow-up phone calls and letters.

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Symptoms measured by RPQ

There was a significant difference, regarding the sum of symptom scores on the RPQ, between the three groups at baseline (df=2, p=0.0004) and at follow-up (df=2, p=0.001) (Kruskal-Wallis test). At baseline, the RPQ sum of symptom scores was significantly greater in the mTBI group compared to the orthopaedic control group (z=-3.03, p=0.002) and to non-injured controls (z=-3.5, p=0.0005) (Mann-Whitney U test). A significant difference was found in the sum of symptom scores at follow-up, between the mTBI group and the orthopaedic control group (z=-2.99, p=0.003), and between the mTBI group and non-injured controls (z=-3.48, p=0.0005) (Mann-Whitney U test). No difference was found between control groups at any time (Mann-Whitney U test). Sum of symptom scores decreased in the mTBI group over time but the difference did not reach statistical significance (z=-1.7, p=0.092) (Wilcoxon signed rank test).

Visual examination

No cranial nerve palsies or direct trauma related eye pathology was found. AI and CI were identified. At baseline, three mTBI patients had combined CI and AI, and nine had AI. At follow-up, one mTBI patient still had CI, and six had AI; five orthopaedic controls had AI at baseline, and six at follow-up. Two non-injured controls with CI and two with AI were found at baseline and at follow-up.

The NPC improved in the mTBI group between baseline and follow-up. Statistical analysis showed a significant interaction effect (df=2, F=3.793, p=0.042) and the ensuing pairwise analysis showed a significant difference for the mTBI group (p=0.015) (Figure 1). There were no significant differences between or within the control groups.

(Insert Figure 1 here)

A significant interaction effect was found for the deviation from expected accommodative amplitude (df=2, F=4.406, p=0.028). The ensuing pairwise analysis showed a significantly greater deviation in mTBI compared to non-injured controls at baseline (p=0.001) (Figure 2). At follow-up six out of 13 mTBI patients still presented with reduced accommodative amplitude, which met the diagnostic criteria for AI. No significant differences in accommodative facility were found within or between groups or test occasions.

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(Insert Figure 2 here)

The analysis of fusional vergence did not show any significant differences at the group level. At baseline, reduced positive fusional vergence (< 20 prism diopters) at near point of focus was found in four mTBI patients, four orthopaedic controls and marginally reduced in two non-injured controls.

Saccade performance

In the pro-saccade task, no significant difference in latency or gain was found between groups or test occasions. No significant differences within or between groups were found in the self-paced saccade task. In the anti-saccade task all groups performed well at both test occasions with no statistically significant differences in latency or proportion of erroneous saccades.

Stereo acuity

All non-injured controls performed 60 seconds of arc or better at both test occasions. In the ortopaedic group three subjects performed 120-240 at baseline and two of these performed similarly at follow-up (one missing). A contrasting finding was that one third (n=5) of the mTBI patients showed crude level of stereo acuity at baseline (120-240) whilst at follow-up, all but one (subject 14, TNO 120), performed 60 or better.

Assessment of visual symptoms

There was a significant difference between the three groups regarding CISS score at the baseline (df=2, p=0.003) (Kruskal-Wallis test). Patients with mTBI had more visual symptoms with near work, compared to the two control groups, as measured by the CISS score at baseline: mTBI vs. orthopaedic controls (z=-2.512, p=0.012) and mTBI vs. non-injured controls (z=-3.092, p=0.02) (Mann-Whitney U test). The median value of the CISS score in the mTBI group at baseline was 24. It then decreased to 19 at follow-up but the change did not reach statistical significance. The CISS score was below cut-off level at both time points in control groups. Vision diagnoses based on optometric assessment of CI or AI were compared with CISS symptoms scores (Table 2). No significant association was found, based on Fisher's exact test. At baseline nine out of 12 mTBI patients with a vision diagnosis were identified using the CISS. Of these 12 patients five had scored two or higher on one or both of the RPQ items concerning blurred or double vision. At follow-up, seven

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mTBI patients still had a vision diagnosis; one with CI and six with AI. Three of these patients scored as symptomatic on CISS. Three of these patients also scored two or greater on RPQ items concerning blurred or double vision, however there was only an overlap for two patients.

Table 2 Vision diagnoses (accommodative– and/or convergence insufficiency) versus CISS and RPQ scores.

Subjects	Examination	Vision diagnosis	CISS < 21	CISS ≥ 21	Score ≥ 2 on RPQ blurred or double vision
mTBI patients	Baseline	No	2	1	-
	n=15	Yes	3	9	5
	Follow-up	No	4	2	1
	n=13	Yes	4	3	3
Orthopaedic controls	Baseline	No	8	1	-
	n=14	Yes	5	-	-
	Follow-up	No	5	1	-
	n=12	Yes	6	-	-
Non-injured controls	Baseline	No	11	-	1
	n=15	Yes	4	-	1
	Follow-up	No	10	1	-
	n=15	Yes	3	1	-

In the mTBI group, CISS scores at baseline correlated with reduced positive fusional vergence measured at near, i.e. the capacity to maintain clear single vision while performing near work (r=-0.6; p=0.02) (Figure 3).

(Insert Figure 3 here)

DISCUSSION

We objectively measured transient visual disturbances in a well-defined mTBI group. We also observed differences in visual measurements between the mTBI group and two control groups.

The patients sustaining a trauma to the head in this study reported significantly more symptoms on the RPQ and CISS compared to both controls groups at baseline. The symptoms decreased at follow-up, but the change was not statistically significant.

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However, the role of brain-injury for these symptoms, especially for patients with long-term problems after mTBI, has been questioned.(35) Several biases have been suggested to affect symptom reporting after mTBI, e.g., recall bias, biopsychosocial factors. Previous studies have demonstrated that similar symptoms also are present after any trauma, presumably due to emotional distress and pain related to the injury.(35, 36) Therefore the scope for this study was on potential objective measures after an mTBI, rather than symptom report. One of the reasons for improvement of self-rated symptom scores might be lack of interest or habituation in filling out a questionnaire.

We found a significant change in NPC in the mTBI group between the baseline and follow-up. Receded NPC has previously been proposed as a potentially sensitive vision-based biomarker after mTBI(14) and our findings tentatively support this. Similar findings in NPC performance were made by Capo-Aponte and co-workers when comparing mTBI patients and controls.(3) However, the median NPC at baseline of these mTBI patients was just within 10 cm, which may or may not be considered clinically meaningful,(15, 32) and therefore not pose a clinical sign for further examination of CI. On the other hand, according to established diagnostic criteria for CI, any NPC greater than six cm is considered insufficient.(32)

The mechanism behind the spontaneous recovery of NPC in the present patient sample remains to be understood. The convergence responses are based on visual processing of binocular disparity and correct ocular motor alignment through vergence eye movements. Given the recovery of NPC, any manifest structural injury affecting motor function (vergence eye movements) can probably be ruled out. Some of the remaining aspects to consider are sensory-motor integration and the ability to respond appropriately to the stimulus. Certain tasks, including the actual test condition for NPC, require that the subject must exert maximal convergence effort to maintain single vision of a very near target. This most likely involves voluntary effort. A question for further discussion is how the constellation of somatic symptoms, cognitive impairments and fatigue, known to be associated with mTBI, may affect the capacity to perform this test optimally. Our clinical observations during this study, along with previous research, suggest that these factors can have contributory effects. (20)

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In accordance to previous studies(3), a significant difference in accommodation between mTBI and each of the control groups at the baseline was found in our study. The mTBI group had a significantly lower accommodative amplitude compared to non-injured controls at the baseline. It then recovered to a certain degree at follow-up, but six mTBI patients still presented with deviations meeting the diagnostic criteria for AI. This corresponds to almost half of the mTBI patients (n=13) who were examined at the follow-up around three months after the injury. To our knowledge there is quite limited research available regarding the expected course of spontaneous improvement. There are some indications that spontaneous recovery may occur up to a year after the injury, but also that AI may be part of persisting issues even long time after the injury.(22, 23) Mechanisms contributing to slow or incomplete spontaneous recovery of accommodation are unclear. Our findings, along with previous observations,(22) indicate the importance of being aware of possible accommodative disorders and theirs effects on the patient's capacity to perform daily activities.

One third of the mTBI patients showed a deficient level of stereo acuity at baseline (120-240), whilst at follow-up all but one performed normally, i.e., 60 or better. These findings may suggest that the visual processing of disparity was particularly affected in the mTBI group. Based on the improvement in stereo acuity we may speculate that underlying factors affecting the ability to resolve and detect stereo disparity, such as inadequate or inefficient vergence and/or accommodative function, improved with time.(37)

We found that mTBI patients had significantly more visual symptoms as measured by CISS score than orthopaedic and non-injured controls. Our findings about reporting visual disturbances at near work after mTBI are consistent with a previous study.(3) We found a significant correlation between CISS score and PFV at near in the mTBI group. This may appear somewhat unexpected since the PFV was normal at group level. The symptom score (CISS) was significantly higher in mTBI than in the control groups. This may be an indication that most mTBI patients were indeed able to perform normally on the PFV, but at a greater effort (causing symptoms). Objective recordings of vergence eye movement have indicated this.(17)

We were not able to replicate the findings of previous studies that found differences in several measures of saccadic eye movements between mTBI patients and controls.

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(3, 7, 13, 25) An explanation could be that changes in saccadic reaction time/latency are subtle, transient, and possibly only to be demonstrated directly after a trauma to the head. In our study, baseline optometric examination took place a few days after mTBI. Our findings are in line with a study of amateur boxers in which saccadic latency was measured at four time points, with baseline before the boxing match (pre-fight), and at 3 days, 7 days and 12 days after-fight, that is after blows to the head (10). Results in this study showed increased saccadic latency directly after the fight; however 12 days later the latency had returned to baseline. The small number of participants and lack of the description of mTBI criteria limit interpretation of findings in that study.

The strength of our study is having two control groups. Traumatic injury can generally impact on reporting of various symptoms, related to acute posttraumatic stress and pain. Therefore, to avoid confounding factors, we included a group of patients with minor orthopaedic injuries without trauma to the head, presenting at the same emergency department.

Study limitations

When the study population is small, there is always a risk for type II error, that is the risk of not revealing a true difference in the studied population. The differences found between mTBI patients and controls regarding oculomotor measures were few and the within group variations were large. The degree of overlap between groups and incomplete correlation between visual symptoms and visual measurements, suggest that caution is appropriate when interpreting findings in an individual patient, based on the current state of knowledge. However, several aspects merit further investigation. The sample size in the present study was based on power calculations from reports on long lasting vision and oculomotor problems in patients after mTBI.(4, 7, 8) To our knowledge there are no another published reports of visual problems including oculomotor changes in the early subacute phases in peer-reviewed journals. Possible bias in these studies could have led to an overestimation of the frequency of oculomotor changes and thus an overestimation of expected effect size in our power calculation and a risk of type II error.

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Study participants were 18-40 years old making the mTBI patient group in this explorative study highly selective. This age limitation was chosen to minimize the effect of presbyopia on study results. Our findings will have relevance regarding the large number of young adults suffering head trauma, but will not be directly applicable to older patients, which limits the generalisability.

Future recommendations

Larger confirmatory studies are needed to clarify the clinical role the transient visual disturbances observed in this study. The role of vergence and accommodation as potential biomarkers for mTBI and their interplay with persisting symptoms such as fatigue also needs further elucidation.

Furthermore, investigations of visual disturbances after mTBI should aim to determine if visual testing in subacute stage after mTBI could help to predict long lasting symptoms and be a target for intervention to promote recovery.

CONCLUSIONS

Some transient measurable visual changes regarding convergence were noted in mTBI patients during the subacute period after injury. The finding of persistent accommodative insufficiency in a substantial proportion of mTBI patients requires further evaluation; this could be either a biomarker for persistent functional impairment in neural networks, or a target for intervention to promote recovery, or possibly both.

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Contributors: GM and JJ contributed to design of the study, were responsible for data collection, wrote initial draft of manuscript, performed statistical analysis, and contributed to the analysis of results and interpretation of findings. CND, TP, MM were main contributors to study design, contributed to data collection, analysis of results and interpretation of the findings. AKG contributed to discussions on study design, critically revised manuscript, and contributed to data analysis and interpretation. All authors read, commented and approved the final manuscript.

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FIGURE LEGENDS

Figure 1 Near point of convergence in mTBI group at baseline and at follow up measured in cm. The lower the value, the better convergence performance. The box indicates median, upper and lower quartile. The whiskers indicate min and max. The x's indicate outliers and miniature squares indicate mean values.

Figure 2 Deviation from expected accommodative amplitude. The lower the negative value, the greater the deviation (insufficiency). Closer to zero is better. The box indicates median, upper and lower quartile. The whiskers indicate min and max. The x's indicate outliers, and miniature squares indicate mean values.

Figure 3 CISS score versus positive fusional vergence in mTBI patients. Higher positive fusion value corresponds to better function.

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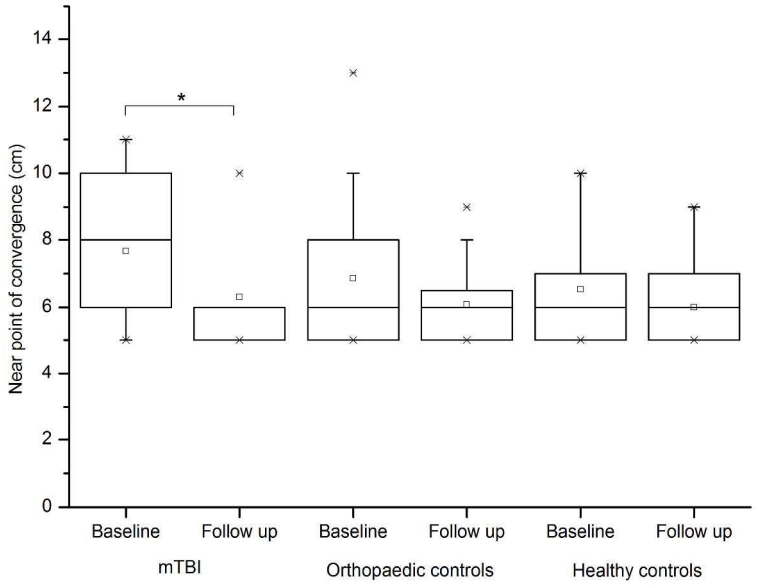

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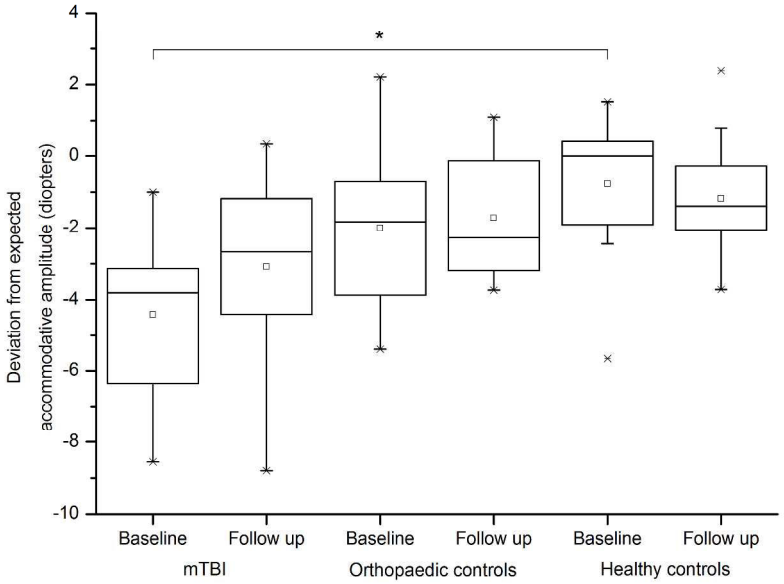

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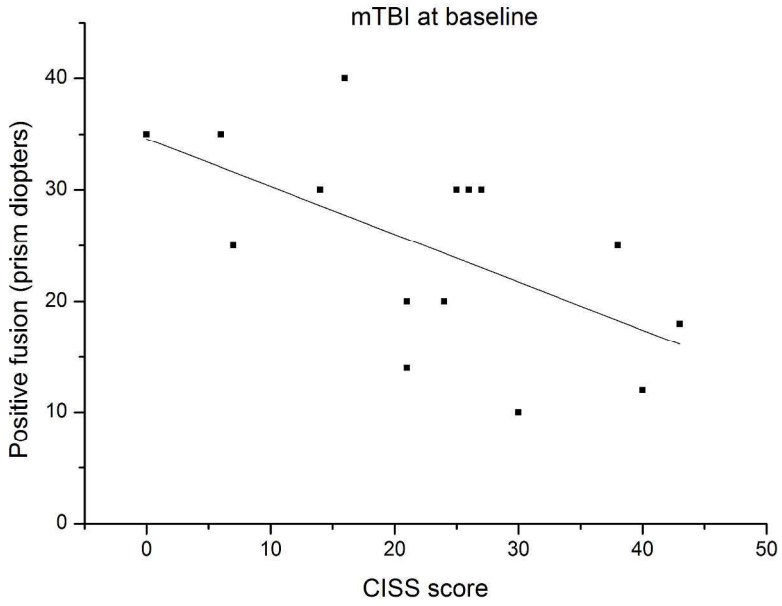

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Research checklist

STROBE Statement - checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable	11-13

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		of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.
NA – not applicable

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BMJ Open

Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury in Sweden– an exploratory prospective observational study

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Neurology
Keywords:	mild traumatic brain injury, visual dysfunction, near point of convergence, accommodation, posttraumatic symptoms, NEUROLOGY

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Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury in Sweden– an exploratory prospective observational study

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ABSTRACT

Objectives: To assess 1) whether visual disturbances can be demonstrated with objective measures more often in patients with mild traumatic brain injury (mTBI) than in orthopaedic controls and non-injured controls, 2) whether such objectively demonstrated disturbances change over time, and 3) whether self-reported visual symptoms after mTBI correlate with objectively measurable changes in visuomotor performance.

Design: A prospective, controlled, observational study, with assessments planned 7-10 and 75-100 days after injury.

Setting: Emergency department of a general hospital in Sweden.

Participants: Fifteen patients with mTBI, 15 patients with minor orthopaedic injury, 15 non-injured controls, aged 18-40 years.

Outcome measures: Visual examination including assessment of visual acuity, accommodation, eye alignment, saccades and stereo acuity. Symptom assessment using Convergence Insufficiency Symptoms Survey (CISS) and Rivermead Post-Concussion Symptoms Questionnaire.

Results: Assessments were performed 2-12 and 81-225 days after injury (extended time frames for logistical reasons). No significant difference was found between the mTBI and control groups regarding pro-saccades, anti-saccades and self-paced saccades at any time point. The accommodative amplitude was significantly lower in the mTBI group compare to non-injured controls at baseline. Six out of 13 patients with mTBI had accommodative insufficiency at follow-up. Near point of convergence in the mTBI group was receded at baseline and improved statistically significantly at follow-up. At baseline, patients with mTBI had significantly higher CISS score than orthopaedic and non-injured controls. For patients with mTBI the CISS score correlated with fusional vergence.

Conclusion: There were some transient measurable visual changes regarding convergence in patients with mTBI during the subacute period after the injury. Our findings of persistence of accommodative insufficiency in a considerable proportion

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of patients with mTBI suggest that this visual function should not be overlooked in clinical assessment.

Key words: neurology, mild traumatic brain injury, visual dysfunction, near point of convergence, accommodation, posttraumatic symptoms.

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ARTICLE SUMMARY

Strengths and limitations of this study

- Prospective longitudinal design with measurement at two time points.
- Strict inclusion criteria for mTBI according to American Congress of Rehabilitation Medicine.
- Inclusion of both an uninjured control group and a group with minor orthopaedic injuries without trauma to the head, to control for non-specific effects of injury such as pain and distress.
- Study methods include several easily replicable optometric measurements.
- The generalisability of this study is limited because the sample of patients with mTBI was small in size and restricted in age range.

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INTRODUCTION

There is a need for objective methods to assess and monitor recovery after mild traumatic brain injury (mTBI), as a base for developing evidence based clinical follow-up guidelines. Changes affecting accommodation and eye alignment have been highlighted recently as possible measurable correlates of symptoms related to mTBI.(1-4) A recent systematic review of oculomotor-based vision assessment to monitor changes after mTBI found preliminary but promising evidence.(5) It was concluded that measurement of oculomotor functions appeared useful in detecting changes after mTBI; however, the strength of evidence in currently available research is not yet sufficient enough to inform clinical guidelines.

Traumatic impact to the head, as in mTBI, may affect vision-related networks that are widely spread throughout the brain,(1, 6) and thus result in visual disturbances. Various visual impairments with a prevalence up to 70 percent have been found in patients with long lasting problems after mTBI.(4, 7, 8) However, these studies have several limitations such as retrospective design, selection bias, heterogeneity regarding severity of injury, and lack of appropriate control groups. Prospective studies with early assessment and follow-up of vision-related oculomotor changes after mTBI are scarce.(9, 10)

The ability to appropriately alter focus, align the eyes, and make gaze changes can be measured, and has been highlighted in several recent studies on mTBI.(11-14) Convergence is a nasalward eye movement for near vision.(15) Insufficient convergence is one of the most frequently described oculomotor changes after head injury.(16) Symptoms after mTBI, both direct visual symptoms (double vision, blurred vision) and indirect symptoms (increased effort at near work), might be attributed to impaired convergence. Convergence insufficiency (CI) was found in 42-48% of patients with mTBI in retrospective studies,(4, 7) and controlled studies of military personnel who have suffered blast-induced mTBI have shown a significant difference in near point of convergence (NPC).(3,7)

Fusional vergence aligns the two eyes and thereby provides for clear single vision. Impaired fusional vergence causes unstable binocular vision, which may present as losing one's place when reading, or blurred, or even double vision. Fusion vergence

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disorders may occur in about 3-6% of an otherwise healthy population with vision-based symptoms,(17, 18) but may be significantly more frequent in traumatic brain injury TBI patients.(19)

Accommodation provides a clear optical image of an object at different distances through the altering of refractive power in the crystalline lens. Symptoms of accommodative disorders include blurred vision and impaired flexibility to alter focus between near and far. A physiological deterioration of accommodative ability, presbyopia, is expected with age. The current study therefore included pre-presbyopic subjects of age 40 or younger. In an otherwise healthy pre-presbyopic population, accommodative changes may be present in up to about 10 % of individuals with vision complaints.(18, 20) Significantly more prevalent accommodative disorders have been found in patients with mTBI in the sub-acute stage,(3) and also as part of persisting issues.(21, 22)

Saccades are rapid eye movements that shift the gaze to areas of interest in the visual field. Through purposeful and accurate saccades executed in quick succession, the environment can be scanned and functional visual field is increased. Thus, an efficient saccadic performance is an important base for efficient and safe interaction with the environment and for detailed work such as reading.(23) The initiation and programming of saccades involves cognitive functions that are subserved by complex neuronal networks involving different parts of the brain. Parameters of saccades, such as latency and accuracy, have been shown to be affected after mTBI.(2, 9, 10, 24)

In this study we aim to assess oculomotor and visual changes after mTBI prospectively, and compare these to a control group unexposed to head injury but with minor orthopaedic injury, and to a non-injured control group. The orthopaedic control group is important for controlling for non-specific effects of pain and distress after trauma to allow evaluation of brain injury specific effects.

The study objectives are to assess: 1) whether visual disturbances can be demonstrated with objective measures more often in patients with mTBI than in orthopaedic controls and non-injured controls, 2) whether such objectively demonstrated disturbances change over time, and 3) whether self-reported visual symptoms after mTBI correlate with objectively measurable changes in visuomotor performance.

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METHODS

This is a prospective controlled observational study on visual disturbances after mTBI, with two control groups, defined below. This article is the first report from this study. The setting was an emergency department (ED) of a large general hospital serving the north-east of Stockholm.

A power calculation was conducted: with an expected incidence of visual disturbances in 70 % in the mTBI group,(4, 7, 8) and 10 % in the control group(18, 20), 10 persons per group were needed to detect visual disturbances with 80 % power at alpha 0.05. With an expected drop out rate of 30 %, 15 persons were needed in each group.

Inclusion criteria

All study participants were 18-40 years of age. Other criteria for each of the three groups were as follows:

1. mTBI group:
    a. Presented to the ED after acute blunt head trauma.
    b. Met diagnostic criteria for mTBI according to American Congress of Rehabilitation Medicine (25): mTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification include: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale (GCS)(26) score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury.
    c. Underwent CT-brain scan on clinical indication.

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2. Orthopaedic control group:
    a. Presented to the ED after minor trauma to the extremities without head trauma.
    b. not requiring surgery.
3. Non-injured control group:
    a. Individuals without traumatic injury, answering an advert recruiting to the study.

Exclusion criteria (any of the following):

a. indication for neurosurgery
b. previous moderate or severe traumatic brain injury
c. any head injury in the previous year requiring medical attention
d. presence of any contraindication for MRI (magnetic resonance imaging)
e. progressive neurological disease or other medical conditions with expected short survival
f. severe visual impairment or manifest strabismus
g. need for help in activities of daily living before the current injury
h. intoxication with alcohol at the time of the injury
i. not fluent in Swedish

For demographic information, see Table 1.

Table 1 Demographic data

	mTBI patients	Orthopaedic controls	Non-injured controls
Age, median (range)	25.0 (18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (%)	14 (93)	N/A	N/A
GCS 14 (%)	1 (7)	N/A	N/A
Type of trauma: n (%)	Fall: 7 (47) Bicycle: 2 (13) Horse back riding: 2(13) Other: 4 (27)	Sports: 9 (60) Other: 6 (40)	

N/A – not applicable, GCS – Glasgow Coma Scale,

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Data collection

Inclusion was conducted between January 2015 and January 2016, and was stopped when a total of 15 patients with mTBI, 15 orthopaedic controls and 15 non-injured controls were included, in accordance with the power calculation. Study patients were contacted by phone 1-3 days after injury. All study participants received written information about the study and gave informed consent.

All data related to the injury, GCS on arrival at the ED, and results of computerised tomography scan (CT-scan), were collected from the medical records. Demographic data were collected by interview at the baseline examination.

All study participants were scheduled to be assessed twice: at baseline, in the subacute phase, (for trauma patients, 7-10 days after the trauma), and at follow-up - 75-100 days after first assessment. Due to recruitment difficulties, and in order to minimize dropout, the time frame for the first and second assessment was extended. The median time between injury and baseline assessment was 6.0 days (range 4-12 days) for patients with mTBI, and 8.0 days, (range 2-9 days) for orthopaedic controls. The median time between baseline and follow-up was 95 days (range 81-225) for patients with mTBI, and 108 days (range 87-324) for orthopaedic controls. No significant difference was found between patients with mTBI and the orthopaedic control group regarding time between the injury and assessments (baseline and follow-up).

Neuropsychological testing and visual assessment were performed at different time points on the same day or on the day before or after.

Patients with mTBI and orthopaedic controls underwent examination with structural magnetic resonance imaging (MRI) and resting state functional MRI of the brain at baseline and at follow-up. All participants rated anxiety, depression and fatigue using Hospital Anxiety and Depression Scale (HADS)(27) and Fatigue Severity Scale (FSS),(28) and underwent neuropsychological testing. These data and imaging results will be reported separately.

Among the consecutive patients who were invited to participate in the study, a total of ninety-nine declined; 17 mTBI and 82 orthopaedic subjects. Of those who declined, 88 % of mTBI and 64 % of orthopaedic subjects were men, and there was no difference regarding age between participating and non-participating individuals. The reasons stated for not participating were lack of time and inconvenience.

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Two individuals in the mTBI group and two individuals in the orthopaedic control group were lost to follow-up despite several follow-up phone calls and letters.

Assessments

The visual examination was performed by licensed optometrists, using standard optometric clinical methods. It included assessment of visual acuity at far and near, refractive error, stereo acuity, near point of accommodation, facility (flexibility) of accommodation, near point of convergence (NPC) with an accommodative target, non-strabismic eye-turn (heterophoria), eye motility and fusional vergence. Diagnosis of visual dysfunctions were based on established diagnostic criteria.(29) NPC was measured using the push-up method (RAF-ruler). Positive fusional vergence (PFV) was measured with a prism bar. In both cases the patient is instructed to try as hard as possible to maintain single vision and to report when perceiving double vision. Meanwhile, the examiner carefully observes eye alignment in order to verify the patient's response. The expected accommodative amplitude was defined according to the Hofstetter formula (18.5-1/3 age).(29) Diagnosis of accommodative insufficiency (AI) required amplitude less than minimum expected according to the Hofstetter formula (15-1/4 age). Diagnosis of convergence insufficiency (CI) required near point of convergence ≥ 6 cm plus at least one of the following; reduced PFV at near (< 20 prism diopters) or divergent heterophoria at least four prism diopters greater at near than at distance.(29) Saccadic eye movements were recorded (spatial res 0.15 degrees; temporal res 300 Hz) using an eye tracker (Tobii TX300, Tobii Corp., Stockholm, Sweden, www.tobii.com). The participant was positioned 60 cm directly in front of the eye tracker display. Three test paradigms were applied to test (1) visually induced pro-saccades; mean latency and gain, 2) anti-saccades; latency of correctly performed saccades and proportion of erroneous saccades, (3) self-paced saccades; number of saccades performed in 30 seconds and mean intersaccadic interval (ms). The stimuli consisted of a dot with a diameter of 5 mm (0.5 degrees). In the pro-saccade paradigm the participant fixated a centered cross and then re-fixated to a dot that appeared at 2, 4, 6, or 8 degrees to the left or right of the cross. In the anti-saccade paradigm the participant viewed a centered cross and then rapidly looked in the opposite direction to that of a dot presented 8 degrees to the left or right of the centre. In the self-paced saccade paradigm two dots were simultaneously presented for 30 seconds at 8 degrees

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to the left and right of centre. The participant was instructed to move the gaze rapidly, as many times as possible, between the dots.

At baseline and follow-up, all study participants self-rated their symptoms using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ),(30) and the Convergence Insufficiency Symptom Survey (CISS).(31, 32) The RPQ is based on a Likert scale and includes 16 items with ratings: 0 ”no symptoms”, 1 “no more of a problem or transient symptoms”, 2-4 “mild to severe” symptoms. A total sum of all symptom scores (“mild to severe”, excluding ratings of 1) is calculated, with a maximum score of 64. Three or more symptoms after mTBI describes “postconcussional syndrome” in the International Classification of Diseases, 10th revision.(33) The CISS is a validated and reliable instrument(31) that evaluates near work-related visual symptoms. It includes assessment of direct symptoms, such as blur and double vision, as well as indirect symptoms (e.g., difficulty maintaining concentration, sleepiness while reading, headache and ocular discomfort). The survey includes 15 questions with ratings from 0 “never” to 4 “always” for assessment of visual symptoms. The total score is 60 and the cut-off score for abnormal levels of symptoms is 21. This value gives good sensitivity (97.8 %) and specificity (87 %) in otherwise healthy young adults who have presented to optometrists with visual symptoms.(32)

Data analyses

All data were analysed using SPSS 23. Parametric statistics was used for oculomotor measures (accommodation, convergence, fusional vergens and saccades). A two-way repeated measures ANOVA was used for analysing the within-subject factors (baseline vs. follow-up) and the between subject factor (effect of group). Post-hoc tests were performed using Holm-Bonferroni adjustment. Fischer’s exact test was applied for analysis of the categorical data.

Nonparametric Kruskal-Wallis (three groups), Mann-Whitney U (two groups, post-hoc analysis), Wilcoxon sign rank tests and Spearman’s rank correlation were used for comparison of ordinal data from questionnaires (CISS and RPQ). Two-tailed p-values were used with a critical significance level of $p < 0.05$.

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RESULTS

Two of the 15 patients with mTBI had pathological findings on CT-scan of the brain: one had a small subdural haemorrhage and the other a small subarachnoid haemorrhage. Neither required surgery.

Visual examination

No cranial nerve palsies or direct trauma related eye pathology was found.

Accommodation

A significant interaction effect was found for the deviation from expected accommodative amplitude (df=2, F=4.406, p=0.028). The ensuing post-hoc analysis showed significantly reduced accommodative amplitude in the mTBI group compared to non-injured controls at baseline (p=0.001) (Figure 1) but no significant difference between patients with mTBI and orthopaedic controls. There were no significant differences between the mTBI group and either of the control groups at follow-up. Six out of 13 patients with mTBI still had reduced accommodative amplitude at follow-up, which met the diagnostic criteria for AI. No significant differences in accommodative facility were found within or between groups or test occasions.

(Insert Figure 1 here)

Convergence

There were no significant differences between the mTBI group and both control groups at either occasion. NPC improved in the mTBI group between baseline and follow-up. Statistical analysis showed a significant interaction effect (df=2, F=3.793, p=0.042) and the ensuing pairwise analysis showed a significant difference for the mTBI group (p=0.015) (Figure 2). There were no significant differences between or within the control groups.

(Insert Figure 2 here)

Fusional vergence

The analysis of fusional vergence did not show any significant differences at the group level at any time point.

Stereo acuity

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Five out of 15 of the patients with mTBI showed a reduced level of stereo acuity at baseline (120-240 seconds of arc) whilst at follow-up, all but one performed normally (60 seconds of arc or less). In the orthopaedic group three subjects performed at the level of 120-240 seconds of arc at baseline, and two of these performed similarly at follow-up. All non-injured controls performed normally at both test occasions.

Saccade performance

In the pro-saccade task, no significant difference in latency or gain was found between groups or test occasions. No significant differences within or between groups were found in the self-paced saccade task. In the anti-saccade task all groups performed well at both test occasions with no statistically significant differences in latency or proportion of erroneous saccades (ANOVA).

Assessment of visual symptoms

There was a significant difference between the three groups regarding CISS score at the baseline (df=2, p=0.003) (Kruskal-Wallis test). Patients with mTBI had more visual symptoms with near work, compared to the two control groups, as measured by the CISS score at baseline: patients with mTBI vs. orthopaedic controls (U=47.5, p=0.012) and patients with mTBI vs. non-injured controls (U=38.0, p=0.02) (Mann-Whitney U test). The median value of the CISS score in the mTBI group at baseline was 24. It then decreased to 19 at follow-up but the change did not reach statistical significance (Wilcoxon Sign Ranks test). The CISS score was below cut-off level at both time points in the control groups.

At baseline nine out of 12 patients with mTBI were identified with CI/AI using the CISS (Figure 3a). At follow-up, seven patients with mTBI still had CI/AI (Figure 3b); one with CI and six with AI. Three of these patients scored as symptomatic on CISS. However, no association between CISS and CI/AI was found (Fisher's exact test).

(Insert Figure 3 here)

In the mTBI group, CISS scores at baseline correlated with reduced positive fusional vergence measured at near, i.e. the capacity to maintain clear single vision while performing near work (r=-0.6; p=0.02) (Figure 4).

(Insert Figure 4 here)

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Symptoms measured by the RPQ

There was a significant difference, regarding the sum of symptom scores on the RPQ, between the three groups at baseline (df=2, p<0.001) and at follow-up (df=2, p=0.001) (Kruskal-Wallis test). At baseline, the RPQ sum of symptom scores was significantly greater in the mTBI group compared to the orthopaedic control group (U=40.0, p=0.002) and to non-injured controls (U=29.5, p<0.001) (Mann-Whitney U test). A significant difference was found in the sum of symptom scores at follow-up, between the mTBI group and the orthopaedic control group (U=27.0, p=0.003), and between the mTBI group and non-injured controls (U=24.0, p<0.001) (Mann-Whitney U test). Sum of symptom scores decreased in the mTBI group over time but the difference did not reach statistical significance (p=0.092) (Wilcoxon signed rank test).

DISCUSSION

We have observed differences in visual measurements between a well-defined mTBI group and two control groups. We also objectively measured transient visual disturbances in the mTBI group.

In agreement with a previous study(3), a significant difference in accommodation between the mTBI group and each of the control groups at the baseline was found in our study. The mTBI group had a significantly lower accommodative amplitude compared to non-injured controls at baseline. This then recovered to a certain degree at follow-up, but six patients with mTBI still had deviations meeting the diagnostic criteria for AI. This corresponds to almost half of the patients with mTBI (n=13) who were examined at the follow-up around three months after the injury. We know little regarding the expected course of spontaneous improvement in accommodation. There are some indications that AI may be part of persisting issues even in the long term after injury.(21, 22) Therefore it may be necessary to consider therapeutic intervention when appropriate, e.g. spectacle lenses for near work and/or vision therapy.(34)

A somewhat unexpected result was the non-significant difference in NPC between the groups. This is in contrast to findings on NPC performance by Capo-Aponte and co-workers.(3) However, we found a significant change in NPC in the mTBI group between the baseline and follow-up. The mean NPC at baseline of these patients with mTBI was just within 10 cm, which may or may not be considered clinically

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meaningful,(15, 29) and therefore not pose a clinical sign for further examination of CI. Receded NPC has previously been proposed as a potentially sensitive vision-based biomarker after mTBI(14) and our findings tentatively support this.

The mechanism behind the spontaneous recovery of NPC in the present patient sample remains to be understood. The convergence responses are based on visual processing of binocular disparity and correct ocular motor alignment through vergence eye movements. Given the recovery of NPC, any manifest structural injury affecting motor function (vergence eye movements) can probably be ruled out. Some of the remaining aspects to consider are sensory-motor integration and the ability to respond appropriately to the stimulus. Certain tasks, including the actual test condition for NPC, require that the subject must exert maximal convergence effort to maintain single vision of a very near target. This most likely involves voluntary effort. A question for further discussion is how the constellation of somatic symptoms, cognitive impairments and fatigue, known to be associated with mTBI, may affect the capacity to perform this test optimally. Our clinical observations during this study, along with previous research, suggest that these factors can have contributory effects. (19)

One third of the patients with mTBI showed a deficient level of stereo acuity at baseline (120-240 seconds of arc), whilst at follow-up all but one performed normally. These findings may suggest that the visual processing of disparity was particularly affected in the mTBI group. Based on the improvement in stereo acuity we may speculate that underlying factors affecting the ability to resolve and detect stereo disparity, such as inadequate or inefficient vergence and/or accommodative function, improved with time.(35)

We were not able to replicate the findings of previous studies that found differences in several measures of saccadic eye movements between patients with mTBI and controls. (3, 7, 13, 24) An explanation could be that changes in saccadic reaction time/latency are subtle, transient, and possibly only to be demonstrated directly after a trauma to the head. In our study, baseline optometric examination took place a few days after mTBI. Our findings are in line with a study of amateur boxers in which saccadic latency was measured at four time points, with baseline before the boxing match (pre-fight), and at 3 days, 7 days and 12 days after-fight, that is after blows to

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the head (10). Results in this study showed increased saccadic latency directly after the fight; however 12 days later the latency had returned to baseline. The small number of participants and lack of the description of mTBI criteria limit interpretation of findings in that study.

We found that patients with mTBI had significantly more visual symptoms as measured by CISS score than orthopaedic and non-injured controls. Our findings on reported visual disturbances at near work after mTBI are consistent with a previous study.(3) We found a significant correlation between CISS score and PFV at near in the mTBI group. This may appear somewhat unexpected since the PFV was normal at the group level. The symptom score (CISS) was significantly higher in the mTBI group than in the control groups. This may be an indication that most patients with mTBI were indeed able to perform normally on the PFV, but at a greater effort (causing symptoms). Objective recordings of vergence eye movement have indicated this.(36)

The patients sustaining a trauma to the head in this study reported significantly more symptoms on the RPQ and CISS compared to both controls groups at baseline. The symptoms decreased at follow-up, but the change was not statistically significant. However, the role of brain injury for these symptoms, especially for patients with long-term problems after mTBI, has been questioned.(37) Several factors have been suggested to affect symptom reporting after mTBI, e.g., recall bias and biopsychosocial factors. Furthermore, previous studies have demonstrated that similar symptoms are also present after any trauma, presumably due to emotional distress and pain related to the injury.(37, 38) The strength of our study is having two control groups. Traumatic injury can generally impact on reporting of various symptoms, related to acute posttraumatic stress and pain. Therefore, to avoid confounding factors, we included a group of patients with minor orthopaedic injuries without trauma to the head, presenting at the same emergency department.

Study limitations

When the study population is small, there is always a risk for type II error, that is the risk of not revealing a true difference in the studied population. The differences found between patients with mTBI and controls regarding oculomotor measures were few

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and the within group variations were large. The degree of overlap between groups and incomplete correlation between visual symptoms and visual measurements, suggest that caution is appropriate when interpreting findings in an individual patient, based on the current state of knowledge. However, several aspects merit further investigation. The sample size in the present study was based on power calculations from reports on long lasting vision and oculomotor problems in patients after mTBI.(4, 7, 8) Possible bias in these studies could have led to an overestimation of the frequency of oculomotor changes and thus an overestimation of expected effect size in our power calculation and a risk of type II error.

Study participants were 18-40 years old making the mTBI patient group in this explorative study highly selective. This age limitation was chosen to minimize the effect of presbyopia on study results. Our findings will have relevance regarding the large number of young adults suffering head trauma, but will not be directly applicable to older patients, which limits the generalisability.

Future recommendations

Larger confirmatory studies are needed to clarify the clinical relevance of the transient visual disturbances observed in this study. The role of vergence and accommodation as potential biomarkers for mTBI and their interplay with persisting symptoms such as fatigue also needs further elucidation. Furthermore, investigations of visual disturbances after mTBI should aim to determine if visual testing in the subacute phase after mTBI could help to predict long lasting symptoms and be a target for intervention to promote recovery. Our findings, along with previous observations, (21) indicate the importance of not overlooking possible accommodative disorders in the overall assessment of the patient's capacity to return to daily activities.

CONCLUSIONS

Some transient measurable visual changes regarding convergence were noted in patients with mTBI, during the subacute period after injury. The finding of persistent accommodative insufficiency in a substantial proportion of patients with mTBI requires further evaluation; this could be either a biomarker for persistent functional impairment in neural networks, or a target for intervention to promote recovery, or possibly both.

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Contributors: GM and JJ contributed to design of the study, were responsible for data collection, wrote initial draft of manuscript, performed statistical analysis, and contributed to the analysis of results and interpretation of findings. CND, TP, MM were main contributors to study design, contributed to data collection, analysis of results and interpretation of the findings. AKG contributed to discussions on study design, critically revised the manuscript, and contributed to data analysis and interpretation. All authors read, commented and approved the final manuscript.

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Competing interests: None declared.

Patient consent: All patients gave written informed consent.

Ethics approval: Ethics approval was obtained from the Regional ethical review board in Stockholm, diary number 2014/597-31/1. The study adhered to the tenets of the Helsinki Declaration.

Provenance and peer review: Not commissioned, externally peer reviewed.

Data sharing statement: Further data may be available from the authors. Please contact the corresponding author.

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FIGURE LEGENDS

Figure 1 Deviation from expected accommodative amplitude. The lower the negative value, the greater the deviation (insufficiency). Closer to zero is better. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate min and max.

Figure 2 Near point of convergence in the mTBI group at baseline and at follow up measured in cm. The lower the value, the better convergence performance. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate min and max.

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Figure 3 Two-by-two matrix of the association between CI/AI and CISS score at baseline (a) and at follow-up (b).

Figure 4 CISS score versus positive fusional vergence in patients with mTBI. Higher positive fusion value corresponds to better function.

LIST OF ABBREVIATIONS

AI - Accommodative Insufficiency

ANOVA – Analysis of Variance

CI – Convergence Insufficiency

CISS – Convergence Insufficiency Symptoms Survey

CT-scan – computerised tomography scan

ED – emergency department

FSS – Fatigue Severity Scale

GCS – Glasgow Coma Scale

HADS – Hospital Anxiety and Depression Scale

MRI - magnetic resonance imaging

mTBI – mild traumatic brain injury

N/A – not applicable

NPC – Near Point of Convergence

PFV – Positive Fusional Vergence

RAF-ruler – Royal Air Force ruler

RPQ – Rivermead Post-Concussion Symptoms Questionnaire

TBI – traumatic brain injury

TNO - test for stereoscopic vision (The Netherlands Organisation for Applied Scientific Research)

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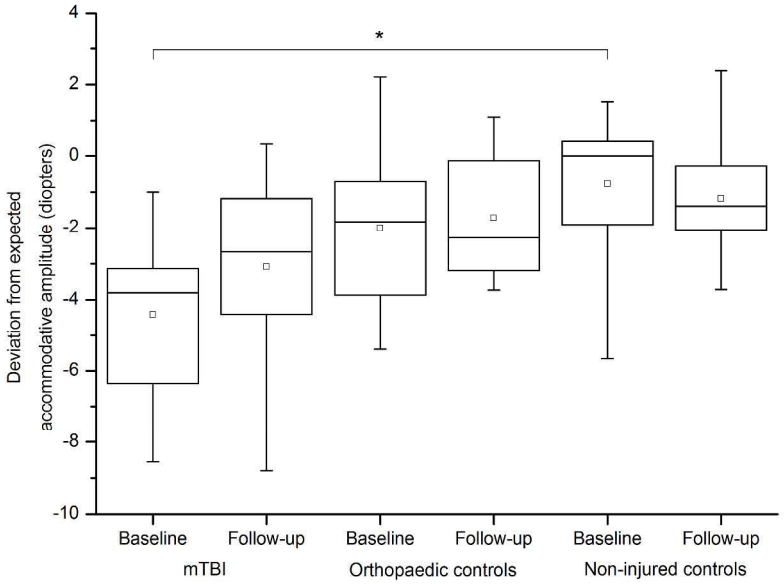

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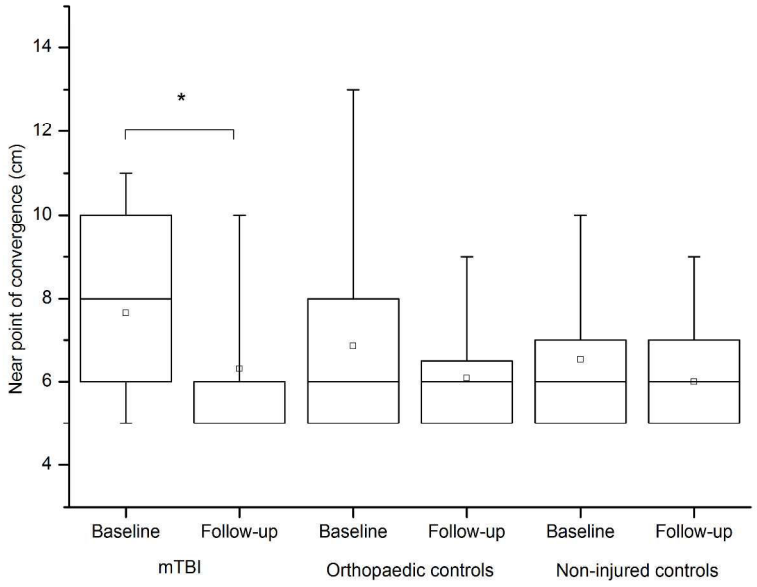

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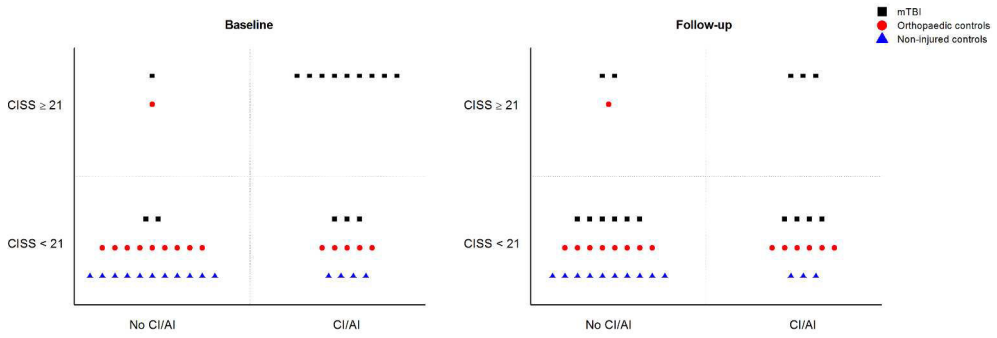

Figure 3 Two-by-two matrix of the association between CI/AI and CISS score at baseline (a) and at follow-up (b).

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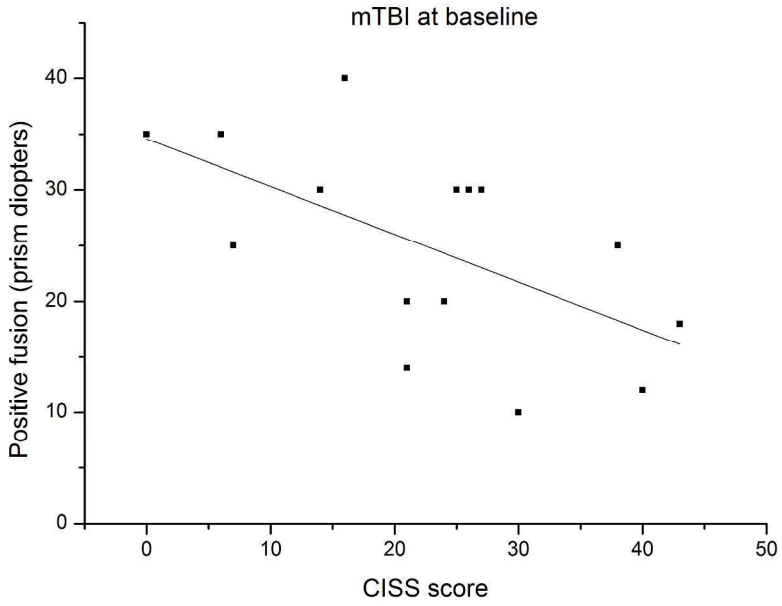

Figure 4 CISS score versus positive fusional vergence in patients with mTBI. Higher positive fusion value corresponds to better function.

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Research checklist

STROBE Statement - checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable	11-13

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		of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.
NA – not applicable

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BMJ Open

Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury in Sweden– an exploratory prospective observational study

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Longitudinal changes in oculomotor function in young adults with mild traumatic brain injury in Sweden– an exploratory prospective observational study

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ABSTRACT

Objectives: To assess 1) whether visual disturbances can be demonstrated with objective measures more often in patients with mild traumatic brain injury (mTBI) than in orthopaedic controls and non-injured controls, 2) whether such objectively demonstrated disturbances change over time, and 3) whether self-reported visual symptoms after mTBI correlate with objectively measurable changes in visuomotor performance.

Design: A prospective, controlled, observational study, with assessments planned 7-10 and 75-100 days after injury.

Setting: Emergency department of a general hospital in Sweden.

Participants: Fifteen patients with mTBI, 15 patients with minor orthopaedic injury, 15 non-injured controls, aged 18-40 years.

Outcome measures: Visual examination including assessment of visual acuity, accommodation, eye alignment, saccades and stereo acuity. Symptom assessment using Convergence Insufficiency Symptoms Survey (CISS) and Rivermead Post-Concussion Symptoms Questionnaire.

Results: Assessments were performed 4-13 and 81-322 days after injury (extended time frames for logistical reasons). No statistically significant difference was found between the mTBI and control groups regarding saccade performance and stereo acuity at any time point. The accommodative amplitude was significantly lower in the mTBI group compared to non-injured controls at baseline. Six out of 13 patients with mTBI had accommodative insufficiency at follow-up. Near point of convergence in the mTBI group was receded at baseline and improved statistically significantly at follow-up. At baseline, patients with mTBI had significantly higher CISS score than orthopaedic and non-injured controls. For patients with mTBI the CISS score correlated with fusional vergence.

Conclusion: There were some transient measurable visual changes regarding convergence in patients with mTBI during the subacute period after the injury. Our findings of persistence of accommodative insufficiency in a considerable proportion

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of patients with mTBI suggest that this visual function should not be overlooked in clinical assessment.

Key words: neurology, mild traumatic brain injury, visual dysfunction, near point of convergence, accommodation, posttraumatic symptoms.

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ARTICLE SUMMARY

Strengths and limitations of this study

- Prospective longitudinal design with measurement at two time points.
- Strict inclusion criteria for mTBI according to American Congress of Rehabilitation Medicine.
- Inclusion of both an uninjured control group and a group with minor orthopaedic injuries without trauma to the head, to control for non-specific effects of injury such as pain and distress.
- Study methods include several easily replicable optometric measurements.
- The generalisability of this study is limited because the sample of patients with mTBI was small in size and restricted in age range.

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INTRODUCTION

There is a need for objective methods to assess and monitor recovery after mild traumatic brain injury (mTBI) as a base for developing evidence based clinical follow-up guidelines. Changes affecting accommodation and eye alignment have been highlighted recently as possible measurable correlates of symptoms related to mTBI.(1-4) A recent systematic review of oculomotor-based vision assessment to monitor changes after mTBI found preliminary but promising evidence.(5) Although measurement of oculomotor functions appears useful in detecting changes after mTBI, the current evidence does not have sufficient strength to inform clinical guidelines.

Traumatic impact to the head, as in mTBI, may affect vision-related networks that are widely spread throughout the brain,(1, 6) and thus result in visual disturbances. Various visual impairments with a prevalence up to 70 percent have been found in patients with long lasting problems after mTBI.(4, 7, 8) However, these studies have limitations such as retrospective design, selection bias, heterogeneity regarding severity of injury, and lack of appropriate control groups. Prospective studies with early assessment and follow-up of vision-related oculomotor changes after mTBI are scarce.(9, 10)

The ability to appropriately alter focus, align the eyes, and make gaze changes can be measured, and has been highlighted in several recent studies on mTBI.(11-14) Convergence is a nasalward eye movement for near vision.(15) Insufficient convergence is one of the most frequently described oculomotor changes after head injury.(16) Symptoms after mTBI, both direct visual symptoms (double vision, blurred vision) and indirect symptoms (increased effort at near work), might be attributed to impaired convergence. Convergence insufficiency (CI) was found in 42-48% of patients with mTBI in retrospective studies,(4, 7) and controlled studies of military personnel who have suffered blast-induced mTBI have shown a significant difference in near point of convergence (NPC).(3,7)

Fusional vergence aligns the two eyes and thereby provides for clear single vision. Impaired fusional vergence causes unstable binocular vision, which may present as losing one's place when reading, or blurred, or even double vision. Fusional vergence

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disorders may occur in about 3-6% of a population with vision-based symptoms who are otherwise healthy.(17, 18) but may be significantly more frequent in traumatic brain injury TBI patients.(19)

Accommodation provides a clear optical image of an object at different distances through the altering of refractive power in the crystalline lens. Symptoms of accommodative disorders include blurred vision and impaired flexibility to alter focus between near and far. A physiological deterioration of accommodative ability, presbyopia, is expected with age. The current study therefore included pre-presbyopic subjects of age 40 or younger. In an otherwise healthy pre-presbyopic population, accommodative changes may be present in up to about 10 % of individuals with vision complaints.(18, 20) Significantly more prevalent accommodative disorders have been found in patients with mTBI in the sub-acute stage(3) and at a later stage as part of persisting issues.(21, 22)

Saccades are rapid eye movements that can direct the gaze to areas of interest in the visual field. Through purposeful and accurate saccades executed in quick succession, the environment can be scanned and functional visual field is increased. Thus, an efficient saccadic performance is an important base for efficient and safe interaction with the environment and for detailed work such as reading.(23) The initiation and programming of saccades involves cognitive functions that are subserved by complex neuronal networks involving different parts of the brain. Parameters of saccades, such as latency and accuracy, have been shown to be affected after mTBI.(2, 9, 10, 24)

In this study we aim to assess oculomotor and visual changes after mTBI prospectively, and compare these to a control group unexposed to head injury but with minor orthopaedic injury and to a non-injured control group. The orthopaedic group allows evaluation of brain injury-specific effects by controlling for non-specific effects of pain and distress after trauma.

The study objectives are to assess: 1) whether visual disturbances can be demonstrated with objective measures more often in patients with mTBI than in orthopaedic controls and non-injured controls, 2) whether such objectively demonstrated disturbances change over time, and 3) whether self-reported visual symptoms after mTBI correlate with objectively measurable changes in visuomotor performance.

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METHODS

This is a prospective controlled observational study on visual disturbances after mTBI, with two control groups, defined below. This article is the first report from this study. The setting was an emergency department (ED) of a large general hospital serving the north-east of Stockholm.

A power calculation was conducted: with an expected incidence of visual disturbances in 70 % in the mTBI group,(4, 7, 8) and 10 % in the control group(18, 20), 10 persons per group were needed to detect visual disturbances with 80 % power at alpha 0.05. With an expected drop out rate of 30 %, 15 persons were judged necessary in each group.

Inclusion criteria

For all study participants, age between 18 and 40 years was a necessary criterion for inclusion. Other criteria for each of the three groups were as follows:

1. mTBI group:
    a. Presented to the ED after acute blunt head trauma.
    b. Met diagnostic criteria for mTBI according to American Congress of Rehabilitation Medicine(25): mTBI is an acute brain injury resulting from mechanical energy to the head from external physical forces. Operational criteria for clinical identification included: (i) 1 or more of the following: confusion or disorientation, loss of consciousness for 30 minutes or less, post-traumatic amnesia for less than 24 hours, and/or other transient neurological abnormalities such as focal signs, seizure, and intracranial lesion not requiring surgery; (ii) Glasgow Coma Scale (GCS)(26) score of 13–15 after 30 minutes post-injury or later upon presentation for healthcare. These manifestations must not be due to drugs, alcohol, medications, caused by other injuries or treatment for other injuries (e.g. systemic injuries, facial injuries or intubation), caused by other problems (e.g. psychological trauma, language barrier or coexisting medical conditions) or caused by penetrating craniocerebral injury.

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c. CT of the brain performed on the basis of clinical need, as assessed by the ED doctor."

2. Orthopaedic control group:
    a. Presented to the ED after minor trauma to the extremities without head trauma.
    b. Did not require surgery.
3. Non-injured control group:
    a. Individuals who had not suffered traumatic injury and who answered an advert recruiting to the study.

Exclusion criteria (any of the following):

a. indication for neurosurgery
b. previous moderate or severe traumatic brain injury
c. any head injury in the previous year requiring medical attention
d. presence of any contraindication for MRI (magnetic resonance imaging)
e. progressive neurological disease or other medical conditions with expected short survival
f. severe visual impairment or manifest strabismus
g. need for help in activities of daily living before the current injury
h. intoxication with alcohol at the time of the injury
i. not fluent in Swedish

For demographic information, see Table 1.

Table 1 Demographic data

	mTBI patients	Orthopaedic controls	Non-injured controls
Age, median (range)	25.0 (18 – 39)	27.0 (18 – 40)	26.0 (19 – 36)
Men, n (%)	7 (47)	11(73)	9 (60)
Women, n (%)	8 (53)	4 (27)	6 (40)
GCS 15 (%)	14 (93)	N/A	N/A
GCS 14 (%)	1 (7)	N/A	N/A

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Type of trauma: n (%)	Fall: 7 (47) Bicycle: 2 (13) Horse back riding: 2(13) Other: 4 (27)	Sports: 9 (60) Other: 6 (40)

N/A – not applicable, GCS – Glasgow Coma Scale,

Data collection

Subject recruitment was conducted between January 2015 and January 2016, and was stopped when a total of 15 patients with mTBI, 15 orthopaedic controls, and 15 non-injured controls were enrolled, in accordance with the power calculation. Study patients were contacted by phone 1-3 days after injury. All study participants received written information about the study and gave informed consent.

All data related to the injury, GCS on arrival at the ED, and results of computerised tomography (CT) of the brain, were collected from the medical records. Demographic data were collected by interview at the baseline examination.

All study participants were scheduled to be assessed twice: at baseline, in the subacute phase, (for trauma patients, 7-10 days after the trauma), and at follow-up - 75-100 days after the injury. Due to recruitment difficulties, and in order to minimize dropout, the time frame for the first and second assessment was extended. Neuropsychological testing and visual assessment were performed at different time points on the same day or on the day before or after. The median time between injury and baseline visual assessment was 7 days (range 4-13 days) for patients with mTBI, and 8 days, (range 7-12 days) for orthopaedic controls. The median time between injury and follow-up visual assessment was 103 days (range 81-232) for patients with mTBI, and 108,5 days (range 87-322) for orthopaedic controls. No statistically significant difference was found between patients with mTBI and the orthopaedic control group regarding time between the injury and assessments (baseline and follow-up).

Patients with mTBI and orthopaedic controls underwent examination with structural magnetic resonance imaging (MRI) and resting state functional MRI of the brain at baseline and at follow-up. All participants rated anxiety and depression using Hospital Anxiety and Depression Scale (HADS)(27), and fatigue using Fatigue Severity Scale (FSS)(28), and underwent neuropsychological testing. These data and imaging results will be reported separately.

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Among the consecutive patients who were invited to participate in the study, a total of ninety-nine declined; 17 mTBI and 82 orthopaedic subjects. Of those who declined, 88 % of mTBI and 64 % of orthopaedic subjects were men, and there was no difference regarding age between participating and non-participating individuals. The reasons stated for not participating were lack of time and inconvenience.
Two individuals in the mTBI group and two individuals in the orthopaedic control group were lost to follow-up despite several follow-up phone calls and letters.

Assessments

The visual examination was performed by licensed optometrists, using standard optometric clinical methods. It included assessment of visual acuity at far and near, refractive error, stereo acuity, near point of accommodation, facility (flexibility) of accommodation, near point of convergence (NPC) with an accommodative target, non-strabismic eye-turn (heterophoria), eye motility and fusional vergence. Diagnosis of visual dysfunctions were based on established diagnostic criteria.(29) NPC was measured using the push-up method (RAF-ruler). Positive fusional vergence (PFV) was measured with a prism bar. In both cases the patient is instructed to try as hard as possible to maintain single vision and to report when perceiving double vision. Meanwhile, the examiner carefully observes eye alignment in order to verify the patient's response. Expected accommodative amplitude was calculated according to the Hofstetter formula (18.5-1/3 age).(29) Diagnosis of accommodative insufficiency (AI) required amplitude less than minimum expected according to the Hofstetter formula (15-1/4 age). Diagnosis of convergence insufficiency (CI) required near point of convergence ≥ 6 cm plus at least one of the following; reduced PFV at near (< 20 prism diopters) or divergent heterophoria at least four prism diopters greater at near than at distance.(29) Saccadic eye movements were recorded (spatial res 0.15 degrees; temporal res 300 Hz) using an eye tracker (Tobii TX300, Tobii Corp., Stockholm, Sweden, www.tobii.com). The participant was positioned 60 cm directly in front of the eye tracker display. We used three test paradigms: (1) pro-saccades; 2) anti-saccades; and (3) self-paced saccades. The stimuli consisted of a dot with a diameter of 5 mm (0.5 degrees). In the pro-saccade paradigm the participant fixated a centered cross and then re-fixated to a dot that appeared at 2, 4, 6, or 8 degrees to the left or right of the cross. The performance was characterised with mean latency and positional gain. In the anti-saccade paradigm the participant viewed a centered cross

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and then rapidly looked in the opposite direction to that of a dot presented 8 degrees to the left or right of the centre. The performance was characterized with the latency of correctly performed saccades and proportion of erroneous saccades. In the self-paced saccade paradigm two dots were simultaneously presented for 30 seconds at 8 degrees to the left and right of centre. The participant was instructed to move the gaze rapidly, as many times as possible, between the dots. The performance was characterised with number of saccades performed in 30 seconds and mean intersaccadic interval (ms).

At baseline and follow-up, all study participants self-rated their symptoms using the Rivermead Post-Concussion Symptoms Questionnaire (RPQ),(30) and the Convergence Insufficiency Symptom Survey (CISS).(31, 32) The RPQ is based on a Likert scale and includes 16 items with ratings: 0 ”no symptoms”, 1 “no more of a problem or transient symptoms”, 2-4 “mild to severe” symptoms. A total sum of all symptom scores (“mild to severe”, excluding ratings of 1) is calculated, with a maximum score of 64. The CISS is a validated and reliable instrument(31) that evaluates near work-related visual symptoms. It includes assessment of direct symptoms, such as blur and double vision, as well as indirect symptoms (e.g., difficulty maintaining concentration, sleepiness while reading, headache and ocular discomfort). The survey includes 15 questions with ratings from 0 “never” to 4 “always” for assessment of visual symptoms. The total score is 60 and the cut-off score for abnormal levels of symptoms is 21. This value gives good sensitivity (97.8 %) and specificity (87 %) in otherwise healthy young adults who have presented to optometrists with visual symptoms.(32)

Data analyses

All data were analysed using SPSS 23. Parametric statistics was used for oculomotor measures (accommodation, convergence, fusional vergence and saccades). A two-way repeated measures ANOVA was used for analysing the within-subject factors (baseline vs. follow-up) and the between subject factor (effect of group). Post-hoc tests were performed using Holm-Bonferroni adjustment. Fischer’s exact test was applied for analysis of the categorical data.

Nonparametric Kruskal-Wallis (three groups), Mann-Whitney U (two groups, post-hoc analysis), Wilcoxon sign rank tests and Spearman’s rank correlation were used

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for comparison of ordinal data from questionnaires (CISS and RPQ) and stereo acuity. Two-tailed p-values were used with a critical significance level of $p < 0.05$.

RESULTS

Two of the 15 patients with mTBI had pathological findings on CT of the brain: one had a small subdural haemorrhage and the other a small subarachnoid haemorrhage. Neither required surgery. No cranial nerve palsies or direct trauma related eye pathology was found.

Visual examinationAccommodation

A significant effect of interaction between group and test occasions was found in the ANOVA for the deviation from expected accommodative amplitude (df=2, F=4.406, p=0.028). The post-hoc analysis showed significantly reduced accommodative amplitude in the mTBI group compared to non-injured controls at baseline (p=0.001) (Figure 1) but no statistically significant difference between patients with mTBI and orthopaedic controls. There were no statistically significant differences between the mTBI group and either of the control groups at follow-up. Six out of 13 patients with mTBI still had AI at follow-up (12 out of 15 patients at baseline) compared to 5 out of 12 orthopaedic controls (no change over time) and 2 out of 15 non-injured controls at follow-up (no change over time). No statistically significant differences in accommodative facility were found within or between groups or test occasions.

(Insert Figure 1 here)

Convergence

The ANOVA showed a significant interaction effect (df=2, F=3.793, p=0.042) and the post-hoc analysis showed a significant difference (improvement) in the mTBI group between baseline and follow-up (p=0.015) (Figure 2). There were no statistically significant differences between or within the control groups.

(Insert Figure 2 here)

Fusional vergence

The ANOVA on fusional vergence did not show any significant differences at the group level at any time point.

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Stereo acuity

No statistically significant difference was found between groups or test occasions regarding stereo acuity (Kruskal-Wallis). Five out of 15 of the patients with mTBI showed a reduced level of stereo acuity at baseline (120-240 seconds of arc) whilst one patient showed a reduced level at follow-up (60 seconds of arc or less). In the orthopaedic group three subjects performed at the level of 120-240 seconds of arc at baseline, and two of these performed similarly at follow-up. All non-injured controls performed normally at both test occasions.

Saccade performance

In the pro-saccade task, no statistically significant difference in latency or gain was found between groups or test occasions (ANOVA). No significant differences within or between groups were found in the self-paced saccade task. In the anti-saccade task all groups performed well at both test occasions with no statistically significant differences in latency or proportion of erroneous saccades.

Assessment of visual symptoms

There was a statistically significant difference between the three groups regarding CISS score at the baseline (df=2, p=0.003) (Kruskal-Wallis test). Patients with mTBI had more visual symptoms with near work, compared to the two control groups, as measured by the CISS score at baseline: patients with mTBI vs. orthopaedic controls (U=47.5, p=0.012) and patients with mTBI vs. non-injured controls (U=38.0, p=0.02) (Mann-Whitney U test). The median value of the CISS score in the mTBI group at baseline was 24. It then decreased to 19 at follow-up but the change did not reach statistical significance (Wilcoxon Sign Ranks test). The CISS score was below cut-off level at both time points in the control groups.

At baseline nine out of 12 patients with mTBI were identified with CI/AI using the CISS (Figure 3). At follow-up, seven patients with mTBI still had CI/AI (Figure 3); one with CI and six with AI. Three of these patients scored as symptomatic on CISS. However, no association between CISS and CI/AI was found (Fisher's exact test).

(Insert Figure 3 here)

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In the mTBI group, CISS scores at baseline correlated with reduced positive fusional vergence measured at near, i.e. the capacity to maintain clear single vision while performing near work (r=-0.6; p=0.02) (Figure 4).

(Insert Figure 4 here)

Symptoms measured by the RPQ

There was a significant difference, regarding the sum of symptom scores on the RPQ, among the three groups at baseline (df=2, p<0.001) and at follow-up (df=2, p=0.001) (Kruskal-Wallis test). At baseline, the RPQ sum of symptom scores was significantly greater in the mTBI group compared to the orthopaedic control group (U=40.0, p=0.002) and to non-injured controls (U=29.5, p<0.001) (Mann-Whitney U test). A significant difference was found in the sum of symptom scores at follow-up, between the mTBI group and the orthopaedic control group (U=27.0, p=0.003), and between the mTBI group and non-injured controls (U=24.0, p<0.001) (Mann-Whitney U test). Sum of symptom scores decreased in the mTBI group over time (median value of the RPQ sum of symptom scores decreased from 22 at baseline to 6 at follow-up), but the difference did not reach statistical significance (p=0.092) (Wilcoxon signed rank test).

DISCUSSION

We have observed differences in visual measurements between a well-defined mTBI group and two control groups. We also objectively measured transient visual disturbances in the mTBI group.

In agreement with a previous study(3), a significant difference in accommodation between the mTBI group and each of the control groups at the baseline was found in our study. The mTBI group had statistically significantly lower accommodative amplitude compared to non-injured controls at baseline. Accommodative amplitude then recovered to a certain degree at follow-up, but almost half of the patients with mTBI still had deviations meeting the diagnostic criteria for AI. We know little regarding the expected course of spontaneous improvement in accommodation. There are some indications that AI may be part of issues even in the long term after injury.(21, 22) Therefore it may be necessary to consider therapeutic intervention when appropriate, e.g. spectacle lenses for near work and/or vision therapy.(33)

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A somewhat unexpected result was the non-significant difference in NPC between the groups. The finding of non-significant differences in NPC among groups is in contrast to that by Capo-Aponte and co-workers.(3) However, we found a significant change in NPC in the mTBI group between the baseline and follow-up. The mean NPC at baseline of these patients with mTBI was just within 10 cm, which may or may not be considered clinically meaningful,(15, 29) and therefore not pose a clinical sign for further examination of CI. Receded NPC has previously been proposed as a potentially sensitive vision-based biomarker after mTBI(14) and our findings tentatively support this.

The mechanism behind the spontaneous recovery of NPC in the present patient sample remains to be understood. The convergence responses are based on visual processing of binocular disparity and correct ocular alignment through vergence eye movements. Given the recovery of NPC, any manifest structural injury affecting motor function (vergence eye movements) can probably be ruled out. Some of the remaining aspects to consider are sensorimotor integration and the ability to respond appropriately to the stimulus. Certain tasks, including the push-up method for measuring NPC used in the current study, require that the subject exert maximal convergence effort to maintain single vision of a very near target. This most likely involves voluntary effort. A question for further discussion is how the constellation of somatic symptoms, cognitive impairments and fatigue, known to be associated with mTBI, may affect the capacity to perform this test optimally. Our clinical observations during this study, along with previous research, suggest that these factors can have contributory effects. (19)

One third of the patients with mTBI showed a deficient level of stereo acuity at baseline (120-240 seconds of arc), whilst at follow-up only one showed deficiency (> 60 seconds of arc). These findings may suggest that the visual processing of disparity was particularly affected in the mTBI group in the acute stage. Based on the improvement in stereo acuity we may speculate that underlying factors affecting the ability to resolve and detect stereo disparity, such as inadequate or inefficient vergence and/or accommodative function, improved with time.(34)

We were not able to replicate the findings of previous studies that found differences in measures of saccadic eye movements between patients with mTBI and controls. (3, 7,

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13, 24) An explanation could be that changes in saccadic reaction time/latency are subtle, transient, and possibly only to be demonstrated directly after a trauma to the head. In our study, baseline optometric examination took place a few days after mTBI. Our findings are in line with a study of amateur boxers in which saccadic latency was measured at four time points, with baseline before the boxing match (pre-fight), and at 3 days, 7 days and 12 days after-fight, that is after blows to the head (10). Results in this study showed increased saccadic latency directly after the fight; however 12 days later the latency had returned to baseline. The small number of participants and lack of the description of mTBI criteria limit interpretation of findings in that study.

We found that patients with mTBI had significantly more visual symptoms as measured by CISS score than orthopaedic and non-injured controls. Our findings on reported visual disturbances at near work after mTBI are consistent with a previous study.(3) We found a significant correlation between CISS score and PFV at near in the mTBI group. This correlation may appear somewhat unexpected since the PFV was normal at the group level. The symptom score (CISS) was significantly higher in the mTBI group than in the control groups. The elevated symptom score may be an indication that most patients with mTBI were indeed able to perform normally on the PFV, but at a greater effort (causing symptoms). Objective recordings of vergence eye movement have demonstrated an association between symptoms and inefficient vergence performance.(35)

The patients sustaining a trauma to the head in this study reported significantly more symptoms on the RPQ and CISS compared to both controls groups at baseline. The symptoms decreased at follow-up, but the change was not statistically significant. However, the role of brain injury for these symptoms, especially for patients with long-term problems after mTBI, has been questioned.(36) Several factors have been suggested to affect symptom reporting after mTBI, e.g., recall bias and biopsychosocial factors. Furthermore, previous studies have demonstrated that similar symptoms are also present after any trauma, presumably due to emotional distress and pain related to the injury.(36, 37) The strength of our study is having two control groups. Traumatic injury can generally impact on reporting of various symptoms, related to acute posttraumatic stress and pain. Therefore, to avoid confounding

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factors, we included a group of patients with minor orthopaedic injuries without trauma to the head, presenting at the same emergency department.

Study limitations

When the study population is small, there is always a risk for type II error, that is the risk of not revealing a true difference in the studied population. The differences found between patients with mTBI and controls regarding oculomotor measures were few and the within group variations were large. The degree of overlap between groups and incomplete correlation between visual symptoms and visual measurements suggest that caution is appropriate when interpreting findings in an individual patient based on the current state of knowledge. However, several aspects merit further investigation. The sample size in the present study was based on power calculations from reports on long lasting vision and oculomotor problems in patients after mTBI.(4, 7, 8) Possible bias in these studies could have led to an overestimation of the frequency of oculomotor changes and thus an overestimation of expected effect size in our power calculation and a risk of type II error.

Study participants were 18-40 years old making the mTBI patient group in this explorative study highly selective. This age limitation was chosen to minimize the effect of presbyopia on study results. Our findings will have relevance regarding the large number of young adults suffering head trauma, but will not be directly applicable to older patients, which limits the generalisability.

Future recommendations

Larger confirmatory studies are needed to clarify the clinical relevance of the transient visual disturbances observed in this study. The role of vergence and accommodation as potential biomarkers for mTBI and their interplay with persisting symptoms such as fatigue also need further elucidation. Furthermore, investigations of visual disturbances after mTBI should aim to determine if visual testing in the subacute phase after mTBI could help to predict long lasting symptoms and be a target for intervention to promote recovery. Our findings, along with previous observations,(21) indicate the importance of not overlooking possible accommodative disorders in the overall assessment of the patient's capacity to return to daily activities.

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CONCLUSIONS

Some transient measurable visual changes regarding convergence were noted in patients with mTBI during the subacute period after injury. The finding of persistent accommodative insufficiency in a substantial proportion of patients with mTBI requires further evaluation. Accommodation insufficiency could be either a biomarker for persistent functional impairment in neural networks, or a target for intervention to promote recovery, or possibly both.

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Contributors: GM and JJ contributed to design of the study, were responsible for data collection, wrote initial draft of manuscript, performed statistical analysis, and contributed to the analysis of results and interpretation of findings. CND, TP, MM were main contributors to study design, contributed to data collection, analysis of results and interpretation of the findings. AKG contributed to discussions on study design, critically revised the manuscript, and contributed to data analysis and interpretation. All authors read, commented and approved the final manuscript.

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Competing interests: None declared.

Patient consent: All patients gave written informed consent.

Ethics approval: Ethics approval was obtained from the Regional ethical review board in Stockholm, diary number 2014/597-31/1. The study adhered to the tenets of the Helsinki Declaration.

Provenance and peer review: Not commissioned, externally peer reviewed.

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Data sharing statement: Further data may be available from the authors. Please contact the corresponding author.

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FIGURE LEGENDS

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Figure 1 Deviation from expected accommodative amplitude. The lower the negative value, the greater the deviation (insufficiency). Closer to zero is better. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate min and max.

Figure 2 Near point of convergence in the mTBI group at baseline and at follow up measured in cm. The lower the value, the better convergence performance. The miniature squares indicate mean values. The box indicates median, upper and lower quartile. The whiskers indicate min and max.

Figure 3 The association between CISS score and the presence of accommodative or convergence insufficiency in patients with mTBI, orthopaedic controls and non-injured controls. The findings at baseline and at follow-up are presented in a two-by-two matrix.

Figure 4 CISS score versus positive fusional vergence in patients with mTBI. Higher positive fusion value corresponds to better function.

LIST OF ABBREVIATIONS

AI - Accommodative Insufficiency

ANOVA – Analysis of Variance

CI – Convergence Insufficiency

CISS – Convergence Insufficiency Symptoms Survey

CT – computerised tomography

ED – emergency department

GCS – Glasgow Coma Scale

MRI - magnetic resonance imaging

mTBI – mild traumatic brain injury

NPC – Near Point of Convergence

PFV – Positive Fusional Vergence

RAF-ruler – Royal Air Force ruler

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RPQ – Rivermead Post-Concussion Symptoms Questionnaire

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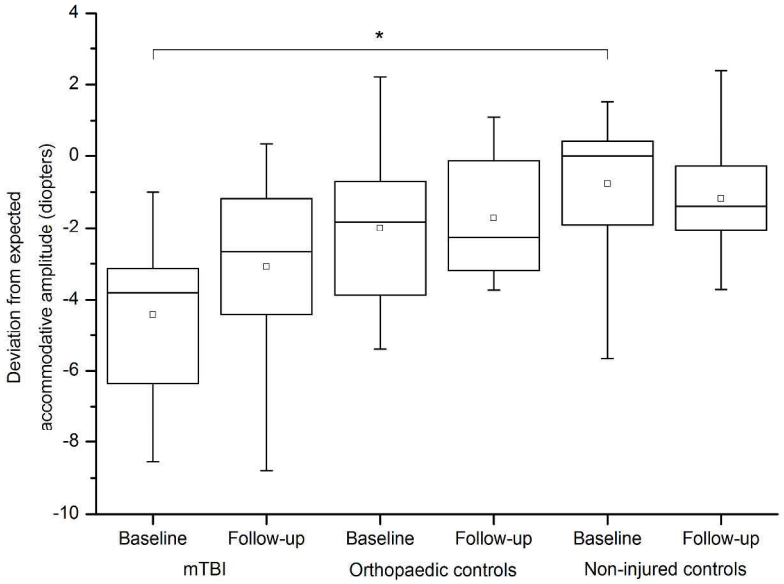

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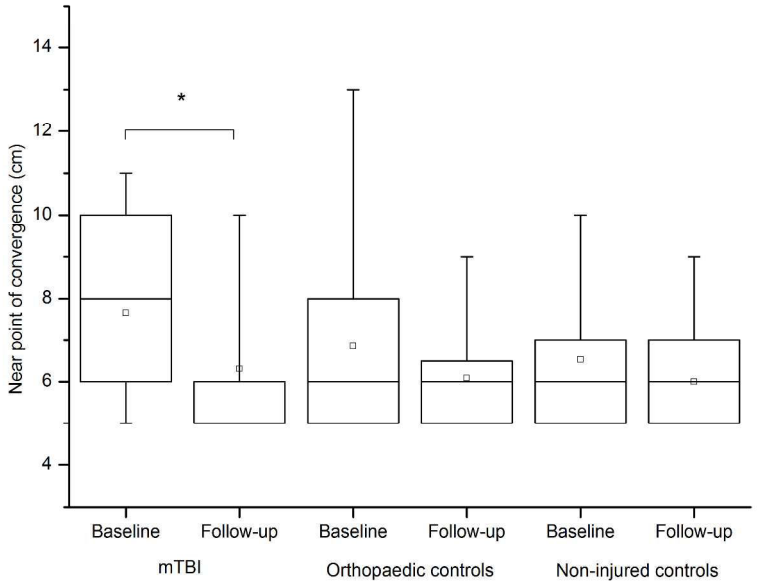

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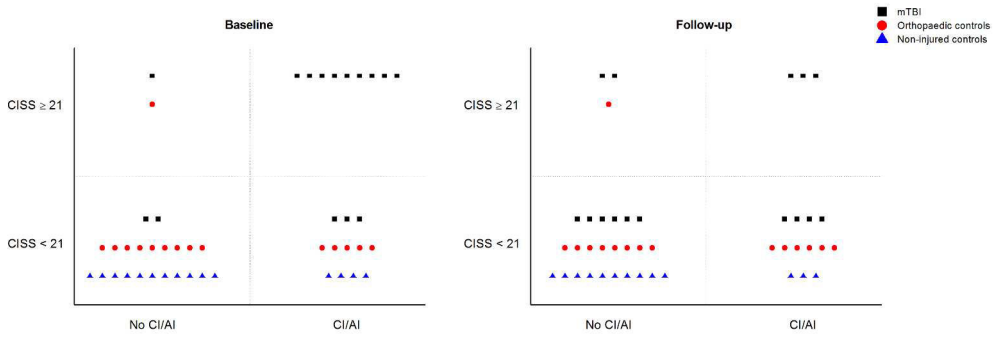

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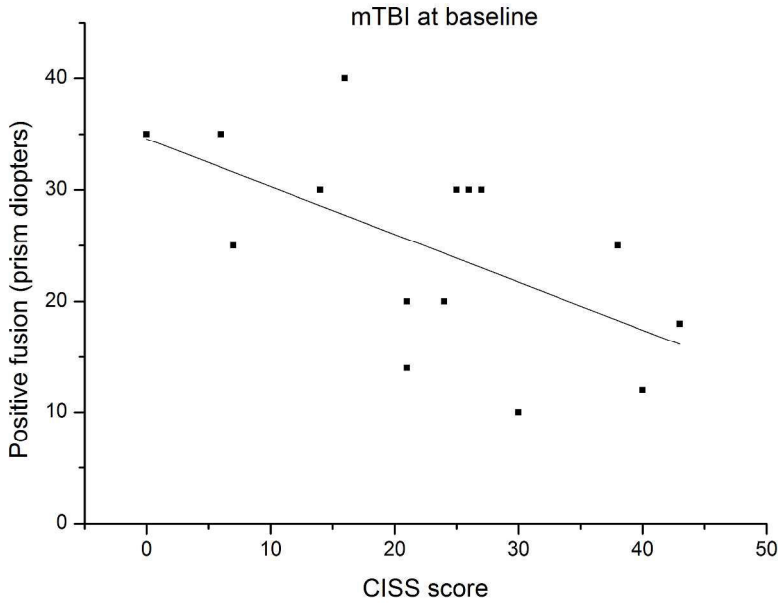

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Research checklist

STROBE Statement - checklist of items that should be included in reports of cohort studies

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-9
Bias	9	Describe any efforts to address potential sources of bias	3
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	9
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, explain how loss to follow-up was addressed	-
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	10
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable	11-13

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		of interest	
		(c) Summarise follow-up time (eg, average and total amount)	10
Outcome data	15*	Report numbers of outcome events or summary measures over time	10-13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10-13
		(*b*) Report category boundaries when continuous variables were categorized	-
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA
Discussion			
Key results	18	Summarise key results with reference to study objectives	14
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-15
Generalisability	21	Discuss the generalisability (external validity) of the study results	16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.
NA – not applicable

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