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Should an increase in cerebral neurochemicals following head kicks in full contact karate influence return to play?

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Abstract

Background: Cerebral neurochemicals are markers of traumatic brain injury (TBI).

Objectives: The aim of the study was to determine whether kicks to the head (KTH) in full contact karate significantly increased serum concentrations of protein S-100B, and neurone specific enolase (NSE). Kicks to the body (KTB) were also quantified to asses muscle tissue injury. Muscle damage was assessed by analysis of serum total creatine kinase (CK).

Methods: Twenty-four full contact karate practitioners were observed and filmed during actual competition and divided into two main groups post event: (1) Kicks to the head and body group (KTH): n = 12; mean ± SD; age, 30.4 ± 6.7 years; height, 1.74 ± 0.1 m; weight, 79.1 ± 2.1 kg; and (2): Kicks to the body group (KTB): n = 12; mean ± SD; age, 28.2 ± 6.5 years; height, 1.75 ± 0.1 m; weight, 79.2 ± 1.7 kg. The KTH group received direct kicks to the head, while group KTB received kicks and punches to the body. Blood samples were taken before and immediately post-combat for analysis of serum S-100B, NSE, CK and cardiac troponin.

Results: Significant increases in serum concentrations of S-100B (0.12 ± 0.17 vs. 0.37 ± 0.26, $\mu g.L^{-1}$) and NSE (11.8 ± 4.1 vs. 20.2 ± 9.1 $ng.mL^{-1}$) were encountered after combat in the KTH group and CK (123 ± 53 vs. 184 ± 103 $U.L^{-1}$) in the KTB group (all $P < 0.05$).

Conclusions: Head kicks in full contact karate cause elevation of neurochemical markers associated with damaged brain tissue. The severity of injury is related to the early post-traumatic release of protein S-100B and NSE. The early kinetics and appearance post injury can reflect intracranial pathology, and suggest S-100B and NSE are extremely sensitive prognostic markers of TBI.

Keywords

concussion, NSE, S100-B, sport, TBI

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Introduction

Karate has never been an Olympic sport but is bidding to be included in the 2020 Olympics.[1] Traumatic brain injury (TBI) as a result of boxing, Taekwondo and Judo, current Olympic combat sports, are potentially dangerous to health.[2]

Approximately 1.5 million individuals with head injuries die every year, with several million receiving emergency treatment. Most of the burden (90%) is in low- and middle-income countries.[3]

Sports' concussive injuries account for approximately 2 million cases per year, in the United States alone, but an appreciation of the symptomatic and cognitive impairments that follow concussion has only been realised within the last decade. This type of injury should be addressed in the management of return-to-play (RTP) or the ability of the individual to perform.[4]

Morbidity and neuropsychological sequelae are very common.[5] Primary care management of the concussed sporting individual should begin immediately post event with analysis of specific neurobiochemical markers of brain damage, such as neurone specific enolase (NSE) and protein S-100B, because their prognostic predictor value of outcome.[6] Patients with specifically high levels of S-100B at initial assessment (>2.5 microg/L) may represent a high-risk group for disability after head trauma.[7]

Routine computerised tomography (CT) or magnetic resonance imaging (MRI) scans of head injuries are not performed in sporting incidents, due to financial constraints and prejudicial views.[8] The analysis of neurochemicals can reduce the need for CT or MRI scans, or admission by over 30%.[9]

Moreover, the routine use of post-head injury surveillance imaging has been considered controversial in terms not only of cost, but also efficacy in identifying those who require operative intervention.[10]

Despite these facts, the determination of neurochemical markers does not appear to be available routinely as either a diagnostic or prognostic markers of cerebral injury in primary or secondary care in the UK. Such information may be useful to set standards where elevations are observed post-head injury, providing a referral system to manage safe and effective return-to-play and prevention of any associated long-term sequelae.

The purpose of this study was to analyse whether kicks to the head (KTH) compared to kicks to the body (KTB), sustained during a karate contest, would result in elevated levels of neurochemical markers, NSE and S-100B, which may indicate cerebral damage. A further analysis was performed within the KTH group to assess if there was a significant difference between technical knockouts (TKOs) compared with kicks to the head, group 2 (KTH2) not resulting in a knock down or technical knockout (TKO).

Muscle damage was quantified by measuring total serum creatine kinase (CK). Cardiac muscle damage was excluded during the competition by the analysis of serum cardiac troponin.

Materials and methods

Subjects

Approval for the study was obtained from the University ethics committee. Prior to data collection all subjects read and completed an informed consent form, which outlined experimental procedures, data collection techniques and the purpose of the study. A pre-competition medical examination on the morning of the event was conducted on all contestants who entered a national full contact karate championship. Data collection procedures comprised of personal interviews, physical examinations and blood analysis. The event comprised four 3-minute rounds. Subjects were all experienced karate practitioners.

Study design

Subjects were divided into four groups, retrospectively following the karate contest, using the standard scoring system, provided by the organisation hosting the event. Tournament rules required a seated judge at each corner of the 10 × 10 m arena and a referee positioned at the centre of the combat arena, who could move anywhere within the arena. Two referee assistants and a match arbitrator were situated outside the competition arena. The tournament rules allowed punches to the body, below the neck, but not the head. However, kicks to the body and the head were permitted.

Measurement of punches and kick

Analysis of punches and KTB and KTH were quantified by the research team on the day of the tournament and further verified by subsequent video

analysis and performance histories obtained from the competitors. A TKO was deemed to have occurred when a competitor was either knocked unconscious, or when receiving a kick to the head, was incapacitated to such an extent, that the central referee ruled that the competitor could not continue.

Following this analysis, male subjects (n = 24) were assigned to: (1) Kicks to the head and body group (KTH): n = 12; mean ± SD; age, 30.4 ± 6.7 years; height, 1.74 ± 0.1 m; weight, 79.1 ± 2.1 kg; and (2) Kicks and punches to the body group (KTB): n = 12; mean ± SD; age, 28.2 ± 6.5 years; height, 1.75 ± 0.1 m; weight, 79.2 ± 1.7 kg.

KTH male subjects (n = 12) were further assigned into two groups: (3) Kicks to the head and body group 2 (KTH2): n = 6; mean ± SD; age, 27.3 ± 7.8 years; height, 1.73 ± 0.1 m; weight, 79.1 ± 2.1 kg; and (4) Technical knockout group (TKO): n = 6; mean ± SD; age, 33.5 ± 3.8 years; height, 1.74 ± 0.1 m; weight, 78.9 ± 1.9 kg.

Subjects acted as their own controls. Physiological tests were performed in the same order for all subjects. Subjects were examined and venous blood samples were taken from the brachial vein, prior to the commencement of combat and within 5 min of cessation.

Values obtained following blood analysis for serum analytes were adjusted to account for plasma volume changes as a consequence of exercise.[11]

Body composition assessment

Total body mass (TBM) was measured using a calibrated beam balance weighing scales (Seca, Cranlea Ltd., Birmingham, UK) and height was measured using a stadiometer (Seca, Cranlea Ltd., Birmingham, UK).

Blood sampling

Venous phlebotomy was conducted, using the standard venepuncture method into vacutainer tubes (Becton Dickinson, Rutherford, NJ, USA). Blood was collected between the hours of 12:00 and 18:00, between 1 and 5 min, of contest completion. Venous blood was collected into an Ethylenediaminetetra-acetic acid (EDTA) vacutainer for assessment of full blood count. Haemoglobin (Hb) concentration was determined using the cyanmethaemoglobin method by placing venous blood in microcuvettes (Haemocue Blood Haemoglobin Photometer, Haemocue Ltd., Sheffield, UK). Packed cell volume (PCV) was measured using a Hawksley Micro-haematocrit Reader (Hawksley & Sons Ltd., West Sussex, UK) following centrifugation at 20,900 g for 4 min in an Analox microhaematocrit centrifuge (Hawksley & Sons Ltd., West Sussex, UK). Hb and PCV blood samples were taken in triplicate and the mean recorded. Bloods were also collected into vacutainers containing serum separation tubes (SST) and lithium-heparin (LiH). LiH tubes were centrifuged at 3500 rpm for 10 min at 4°C. The SST samples were allowed to clot at room temperature for exactly 1 h before centrifugation. The plasma or serum supernatant was removed and placed into tubes (Eppendorf®) and stored at –80°C until analysis. The serum NSE, serum troponin, and serum protein S-100B were all measured by electrochemilluminescent immunoassay using a Modular Analytics E analyser, supplied by Roche Diagnostics; NSE part number: 1213313122; protein S-100B part number: 03175243190.

Total creatine kinase (CK) was measured using a Specord 200 spectrohotometer with a Roche/Hitachi 917/MODULAR P analyser.

Cardiac troponin was measured by electrochemiluminescence immunoassay 'ECLIA' for use on 'Elecsys and cobas e' immunoassay analyser (Roche Diagnostics).

The lower detection limit of the S-100B assay was 0.015 μg/L (0+3 SD) of S-100B protein. The intra-assay variability (CV) was 3.2% at 0.51 μg/L, 2.1% at 5.97 μg/L, and 2.3% at 11.4 μg/L of S-100B protein. The reference value for S-100B in blood was 0.069 ± 0.058 μg/L.

The lower detection limit of the NSE assay was 1 μg/L (0+3 SD). The intra-assay variability (CV) was 2.99% at 10.3 μg/L, 4.7% at 83.7 μg/L and 2.0% at 184 μg/L NSE. The reference value for NSE in blood was 11.1 ± 4.7 μg/L.

The assays for CK and cardiac troponin showed excellent between-run precision (co-efficients of variation = 3.3–4.9%).

Statistical analysis

Data were analysed using the PASW 21.0 for Windows statistical package. Parametric data analysis is presented as mean ± standard deviation (SD) and analysed using Student's t-test. Non-parametric

Table 1. Subject characteristics including pre- and post-bout outcomes for KTH and KTB.

Variable	KTH (Pre-bout) (n = 12)	KTH (Post-bout) (n = 12)	KTB (Pre-bout) (n = 12)	KTB (Post-bout) (n = 12)
Age (years)	30.4 ± 6.7	30.4 ± 6.7	28.2 ± 6.5	28.2 ± 6.5
Height (m)	1.74 ± 0.1	1.74 ± 0.1	1.75 ± 0.1	1.75 ± 0.1
Body mass (kg)	79 ± 2.1	79 ± 2.1	79.2 ± 1.7	79.2 ± 1.7
CK ($U.L^{-1}$)	160 ± 88	186 ± 101	123 ± 53	184 ± 103*
S100B ($ug.L^{-1}$)	0.12 ± 0.17	0.37 ± 0.26†‡	0.12 ± 0.16	0.11 ± 0.12
NSE ($ng.mL^{-1}$)	11.8 ± 4.1	20.2 ± 9.0†	13.8 ± 6.1	17.5 ± 7.4

*Within the KTB group, CK increased post trauma: $P < 0.05$.
†Within the KTH groups, the S100B and NSE increased post trauma: $P < 0.05$.
‡$P < 0.05$ = significantly different to KTB.
CK: creatine kinase; KTB: kicks to the body group; KTH: kicks to the head group; NSE: neurone specific enolase.

data are described as median and inter-quartile range, and analysed using the Wilcoxon rank-sum test. Group differences were analysed using a two-way (group x time) repeated measures ANOVA. Between-group differences were analysed using an independent t-test with an α level set at the $P < 0.05$ for significance. Within group differences were analysed using a paired t-test followed by a post-hoc Bonferroni α level set at $P < 0.017$ for significance. All t-tests were two-tailed.

Results

Following the karate contests, significant increases ($P < 0.05$) in serum concentrations of S-100B, and NSE were encountered in the KTH group, but not in the KTB group. S-100B was significantly increased in KTH group, versus the KTB group, but not NSE.

Serum CK was significantly elevated ($P < 0.05$) in KTB group (Table 1). There were no elevated levels of serum cardiac troponin.

There were significant increases ($P < 0.05$) in serum concentrations of S-100B, and NSE in the TKO group and the KTH2 group (Figures 1 and 2). S-100B was also significantly increased post combat in both the TKO group and the KTH2 group versus the KTB group (Table 2).

There was no further significant increase in the TKO group versus the KTH2 group. However Cohen's *d* analysis[12] of S-100B, in TKO vs. KTH2 demonstrated a large increase (31%) and a medium effect size (0.47), whereas there was no difference in effect size in NSE between the two groups (Table 2). All TKOs were provided with head injury advice and advised to attend hospital. One subject who incurred a knockout was taken to hospital by ambulance.

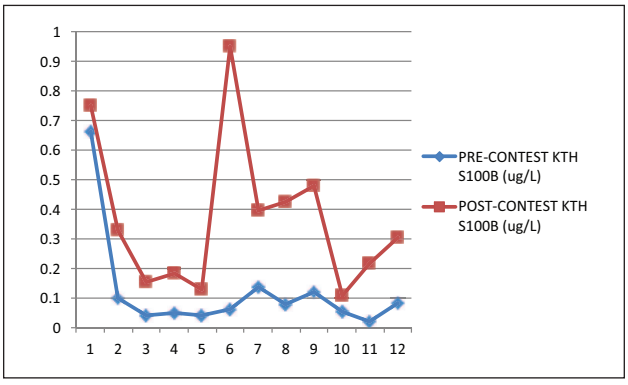

Figure 1. Individual differences in protein S-100B ($\mu g.L^{-1}$) pre-contest and post-contest, following four 3-min rounds of karate (n = 12).
Y-Axis: Protein S-100B ($\mu g.L^{-1}$).
X-Axis: Individual subjects (n = 12).
Pre-contest kicks to the head (KTH) protein S-100B ($\mu g.L^{-1}$) = pre-contest KTH, S-100B.
Post-contest KTH protein S-100B ($\mu g.L^{-1}$) = post-contest KTH, S-100B.

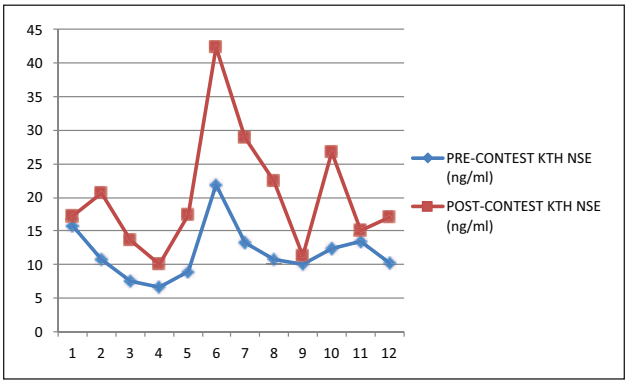

Figure 2. Individual differences in neurone specific enolase (NSE) ($ng.mL^{-1}$) pre-contest and post-contest, following four 3-min rounds of karate (n = 12).
Y-Axis: NSE ($ng.mL^{-1}$).
X-Axis: Individual subjects (n = 12).
Pre-contest kicks to the head (KTH) NSE ($ng.mL^{-1}$) = pre-contest KTH, NSE.
Post-contest KTH NSE ($ng.mL^{-1}$) = post-contest KTH, NSE.

Table 2. Subject characteristics including pre- and post-bout outcomes for TKO, KTH and KTB.

Variable	TKO (Pre-bout) (n = 6)	TKO (Post-bout) (n = 6)	KTH2 (Pre-bout) (n = 6)	KTH2 (Post-bout) (n = 6)	KTB (Pre-bout) (n = 12)	KTB (Post-bout) (n = 12)
Age (years)	33.5 ± 3.8	33.5 ± 3.8	27.3 ± 7.8	27.3 ± 7.8	28.2 ± 6.5	28.2 ± 6.5
Height (m)	1.74 ± 0.1	1.74 ± 0.1	1.73 ± 0.1	1.73 ± 0.1	1.75 ± 0.06	1.75 ± 0.06
Body mass (kg)	78.9 ± 1.9	78.9 ± 1.9	79.1 ± 2.1	79.1 ± 2.1	79.2 ± 1.7	79.2 ± 1.7
Body mass index ($kg.m^2$)	26.1 ± 0.6	26.1 ± 0.6	26.4 ± 0.7	26.4 ± 0.7	25.9 ± 0.6	25.9 ± 0.6
S100B ($ug.L^{-1}$)	0.16 ± 0.25	0.42 ± 0.3*†	0.08 ± 0.04	0.32 ± 0.14*†	0.12 ± 0.1	0.16 ± 0.1
NSE ($ng.mL^{-1}$)	11.9 ± 5.9	20.2 ± 11.4*	11.7 ± 1.5	20.2 ± 6.9*	13.8 ± 6.1	17.5 ± 7.4

*Within the TKO and KTH2-groups the S100B, NSE increased post trauma: $P < 0.05$.
†$P < 0.05$ = significantly different to KTB.
CK: creatine kinase; KTB: kicks to the body group; KTH2: kicks to the head group 2; NSE: neurone specific enolase; TKO: technical knockout group.

Discussion

In this study, the serum elevation of brain neurochemicals, resulting from head trauma, concurred with past studies which have shown a significant increase and correlation between the neurochemical markers, NSE and S-100B after traumatic brain injury (TBI)[13] and in boxing by the research group.[14] These data also concurred with work performed in head injuries in other combat sports.[15] The significant difference in S-100B between the KTH, KTH2 and TKO groups versus KTB group correlated with work done by others, which suggested that S-100B might be a more sensitive neurochemical marker for cerebral trauma than NSE.[16]

Serum CK was significantly elevated ($P < 0.05$) in the KTB group but not the KTH group, indicating the adverse effect from skeletal muscle trauma as a consequence of body kicks and punches (Table 1). There were no elevated levels of serum cardiac troponin, indicating all competitors had healthy hearts prior to the commencement of the competition.

Repeated head trauma that is experienced in contact sport may lead to the development of dementia pugilistica (DP) or punch-drunk syndrome. The molecular markers present in the plaques and tangles of DP are the same as those in Alzheimer's disease (AD).[17]

TBI primarily directly affects neurons, blood vessels and glia, resulting in complex cellular, inflammatory, neurochemical and metabolic alterations. Subsequently investigation in neurochemical markers following TBI provided prognostic markers and management of the effects of trauma.[18]

Protein S-100B (a glial marker) and NSE (a neuronal marker) were the most frequently investigated biomarkers in clinical research due to their detectability in serum. The S-100B protein cytokine is a calcium-binding protein and is physiologically produced and released predominantly by astrocytes in the central nervous system (CNS). It is present in the cytosol of glial and Schwann cells. NSE is predominantly found in the cytoplasm of neurons and in cells with neuroendocrine differentiation. Increased concentrations of NSE and S-100B can both be measured in cerebrospinal fluid (CSF)[19] and in peripheral blood after cerebral trauma and are accurate predictors of outcome, S-100B being more sensitive than NSE.[20] Acute measurement of NSE and S-100B serum concentrations may provide a quantitative predictor of outcome after TBI in young children, which can be extrapolated to adults.[21]

S-100B has multiple functions including the inhibition of protein phosphorylation through interacting with kinase substrates, regulating enzyme activity and interacting with cytoskeletal elements. It is also involved in calcium homeostasis and is believed to have a role in cytosolic calcium buffering. It has been shown to be raised in many organic brain disorders such as TBI, subarachnoid haemorrhage, stroke, epilepsy, multiple sclerosis, Parkinson's disease and hydrocephalus. In addition, there is clinical and laboratory evidence that it is raised in certain neuropsychiatric disorders including post-traumatic stress disorder. S-100B has great potential to become a specific neurological screening tool that is predictive of outcome and responsive to treatment.[22]

Secondary changes of TBI can include axonal injury, reduced cerebral blood flow, decreased cerebral cell glucose uptake, oedema, raised intracranial pressure (ICP), increased blood-brain barrier (BBB) permeability, elevated oxidative stress

(from increased free radical production), excitatory neurotransmitter release, inflammation and cell death.[23]

A suggested mechanism of TBI-induced cell damage is of excess free radical generation produced by mitochondria. During normal metabolism, the tricarboxylic acid cycle (TCA) generates reducing equivalents to produce adenosine triphosphate (ATP). Electrons are normally transferred along the electron transport chain, with only 1–2% of the oxygen generating oxygen radicals at Complex I in the respiratory chain. However, following TBI, changes in the availability of these reducing equivalents is diminished and the production of the superoxide anion (O_2^-) is increased. Following a TBI intracellular calcium (Ca^{2+}) increase activates specific enzymes, such as xanthine dehydrogenase, phospholipase A2 and nitric oxide synthase (NOS), which increase O_2^- and nitric oxide anion (NO) production, which can result in oxidative damage.[24,25]

Classification of TBIs begins at the scene of an incident and can be mild, moderate or severe and the Glasgow coma scale (GCS) is the most commonly used system. This measures a patient's level of consciousness based on verbal, motor and eye-opening responses after injury and defines clinical severity. A GCS score of 3–8 (out of 15) is considered a severe TBI, 9–12 (out of 15) is moderate, and 13–15 (out of 15) is considered a mild TBI.[26] Prior to identification of the neurochemical markers it was a very accurate predictor of outcome and no patient did significantly better than expected.[27]

In this cohort, one individual who received a direct kick to the head, suffered a knockout and endured a tonic-clonic seizure. GCS was recorded as 3/15 (E1, V1, M1) (Table 3). Full paramedical management was initiated. Because of the serious nature of the injury post combat, blood sampling by the research team was not possible.

On regaining consciousness, the GCS recorded at 6 min was 13/15 (E4, V4, M5) (Table 3). Examination of central nervous system (CNS) revealed left sided hyper-reflexia and a left upgoing plantar response. A GCS score of 8 or less suggests a severe brain injury[26] and the participant was admitted to the nearest hospital, known to have a neurosurgical unit.

The patient was discharged without any blood tests or CT scans, despite a letter being presented requesting a neurosurgical opinion.

Table 3. Glasgow Coma Scale: Individual subject readings.[26]

Time post trauma	1 min	4 min	6 min
Score	3	4	13
Best eye response (max 4)			
1. No eye opening	✓		
2. Eye opening to pain		✓	
3. Eye opening to verbal command			
4. Eyes open spontaneously			✓
Best verbal response (max 5)			
1. No verbal response	✓	✓	
2. Incomprehensible sounds			
3. Inappropriate words			
4. Confused			✓
5. Orientated			
Best motor response (max 6)			
1. No motor response	✓	✓	
2. Extension to pain			
3. Flexion to pain			
4. Withdrawal from pain			
5. Localising pain			✓
6. Obeys commands			

Because of the occurrence of the seizure, the authors believed that he should have been admitted for 12 h for neurological observation or received a CT scan of his brain.

All knockouts in karate should be treated as serious head injuries and all subjects should be advised to attend hospital and, if warranted, conveyed to hospital. The GCS is still the most commonly used assessment in the field; however, following admission to hospital research indicates that it should be superseded by the 'Full Outline of Unresponsiveness (FOUR) score' which is a more accurate predictor of discharge outcome in TBI patients.[28]

Post-TBI concussive symptoms can be divided into three areas: (1) somatic, e.g. headaches; (2) emotional (behavioural), e.g. personality changes; and (3) cognitive, e.g. decreased mental acuity.[29]

Such sequelae may be permanent and compounded by the fact that athletes seldom report concussive symptoms, which makes the diagnosis and management challenging. The pathophysiology of concussion requires traditional management, and categorisation and return-to-play guidelines should be for individual assessments and management. Once diagnosed with a concussion, a sportsperson must not be allowed to return-to-play before the concussion symptoms have completely resolved.[30] Neuropsychological testing may also be used in such management to prevent any decreased neurocognitive functioning.[31]

The improved nutrition, training regimes and fitness in competitive sporting individuals over the last century has resulted in physiques that can generate increased pace and therefore concussive forces, following TBIs. The incidence of TBIs in sport has dramatically increased resulting in socioeconomic deficits owing to any ensuing disability.

Even a single mild TBI can lead to impaired function.[32]

There is a duty of care by professionals within different sporting disciplines to manage acute and any potential long-term consequences of brain injury.

Adding the measurement of S-100B serum concentration to the clinical decision rules for a CT scan or hospitalisation in patients with mild TBI could allow a 30% reduction in scans and in hospitalisation for clinical observation.[33]

Research suggests that patients with severe and moderate TBI and post-concussion syndrome should be managed in multidisciplinary neuroscience centres, regardless of the need for neurosurgical intervention to improve outcome.[34]

In conclusion, a recent review provided evidence that cognitive function only improved in the month after mild TBI (MTBI) and that verbal learning can be impaired up to 6 months after MTBI. Evidence also exists that MTBI is associated with a significant increase in the incidence of psychiatric disorders, and a three-fold increase in the risk for suicide.[35] The extrapolation of the effects of management of even MBTI influencing return to play policies in sport requires serious consideration, further investment and research.[36]

The recent increased attention in the media and medical profession regarding the sequelae of MTBI, suggests the requirement of an expert neurological report including serial neurochemical markers (a 'neurobiological passport') prior to return-to-play in cases with clinical symptoms of impaired cognitive function and elevated post-concussive neurochemicals following MBTI, as a minimum.

Following MBTI, serum neurochemicals can remain elevated for several weeks, but every case is different and the exact time to return to baseline is unknown. The authors also advocate the addition of another even greater predictive neurochemical biomarker (total tau, a protein signalling axonal damage in the brain) be added to this passport.[37] This may assist future psychological and pharmacological rehabilitation at primary and secondary care level.

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