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The Final thesis

LONG-TERM SEQUELAE AFTER MILD HEAD INJURY

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(title)

Students‘ (name, surname), group _____Jana Matzen, Group 4_____

Department/ Clinic _____Neurology and Neurosurgery _____

Supervisor _____Dr. Gunaras Terbetas_____

(signature)

Consultant (if applicable) _____

(signature)

The Head of Department/Clinic _____Prof. Dr. Dalius Jatuzis_____

(signature)

Registration day at Department/Clinic_____

(filled in by technical assistant of Department/Clinic)

Registration n._____

(filled in by technical assistant of Department/Clinic)

Email of the student_____jana.matzen@mf.stud.vu.lt_____

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SUMMARY

Post-concussive syndrome, second impact syndrome and chronic traumatic encephalopathy belong to the long-term sequelae after mild traumatic brain injury. Even though a lot of research exists, some sources describe contradictory findings, as these phenomena are still rarely seen, and the spectrum of reported symptoms and clinical findings is quite broad. As a consequence, definitions, predisposition factors, time span of symptoms, diagnostic criteria, pathophysiology, and treatment possibilities are yet hard to define as multiple have been proposed but are yet hard to be verified by definite evidence.

The main risk group seems to be contact sport players and military personnel. Post-concussive syndrome includes physical, cognitive, behavioural, and emotional symptoms, which persist longer than typical post-concussive symptoms. Second impact syndrome describes the occurrence of a second head injury before complete recovery from the first one. Patients often report post-concussive symptoms after the first injury, followed by a collapse and coma after the second injury with the presence of diffuse cerebral edema. Post traumatic encephalopathy, also termed chronic traumatic encephalopathy describes a progressive neurological deterioration caused by repetitive brain trauma including an accumulation of pathologic tau protein and neurofibrillary tangles. Diagnosis depends on the possibilities of the medical center and involves gathering of anamnestic data, the subjective description of symptoms, conventional imaging like CT and MRI and if available, specific laboratory biomarkers and specific brain imaging like susceptibility weighted imaging, diffusion tensor imaging, MR spectroscopy, PET and functional MRI. For management options, there are multiple proposed experimental medical therapies, but the most effective seems to be prevention of multiple injuries, next to rest, rehabilitation with low-level (aerobic) exercise and a prolonged time period until returning to sports/work. In the case of second impact syndrome, the main goal is the reduction of the raised intracranial pressure and avoidance of deathly complications like brain herniation.

ABBREVIATIOINS

WHO: World Health Organization

TBI: Traumatic Brain Injury

MTBI: Mild Traumatic Brain Injury

ICD-10: International Classification of Disease-10

DSM-V: Diagnostic and Statistical Manual of Mental disorders-5

PCS: Post Concussive Syndrome

CTE: Chronic traumatic encephalopathy

AD: Alzheimer's disease

RPQ: Rivermead post-concussion symptoms questionnaire

IL: Interleukin

TNF: Tumour necrosis factor

FUS: focused ultrasound

LIPUS: low-intensity pulsed ultrasound

KEYWORDS

post concussive syndrome, second impact syndrome, mild traumatic brain injury, neurological sequelae, long term outcome of mild head injury, neurobehavioral sequelae, Post traumatic Encephalopathy, Chronic traumatic encephalopathy

INTRODUCTION

In this thesis, a literature review will be performed about the incidence, possible predispositions, pathogenesis, clinical picture, diagnostic possibilities, and management of long-term sequelae after mild traumatic brain injury, including post concussive syndrome, second impact syndrome and chronic traumatic encephalopathy.

There are multiple definitions of mild traumatic brain injury. The most widely used definition for a long time was the one from 1993, when the American Congress of Rehabilitation Medicine defined mild traumatic brain injury as a traumatically induced physiological disruption of brain function manifested by at least one of the following diagnostic criteria:

- Any loss of consciousness
- Any loss of memory of events immediately before or after accident
- Any alteration in mental state at time of accident
- focal neurological deficits (may or may not be transient)

but with it's severity not exceeding:

- Glasgow coma scale score of 13 to 15 at 30 minutes after injury
- loss of consciousness for up to 30 minutes
- posttraumatic amnesia for less than 24 hours (1)

In 2003, the WHO Collaborative Center Task Force on Mild Traumatic Brain Injury published a review of existing definitions and identified several discrepancies for example involving different Glasgow Coma scale scores or different duration of loss of consciousness (2). Therefore, the WHO task force found an adapted version of the AMCR definition as written below:

„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 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 "(3) (p.115)

Ruff et. al further explain the difficulties of finding one standardized definition of mild traumatic brain injury because of rapid resolution of symptoms and typical absence of objective evidence like signs of injury on neuroimaging (2).

With this primary definition of mild traumatic brain injury and its diagnostic criteria already being difficult to standardize, one can imagine, that finding a definition and confirming the diagnosis of long-term sequelae after mild traumatic brain injury can also be complicated. As most patients recover quickly within days, weeks, or months, it is not clearly understood, why some people have poorer outcomes and long-term sequelae. Long-term sequelae after mild traumatic brain injury include:

- Neurobehavioral sequelae: spectrum of somatic and neuropsychiatric symptoms. Similar to post concussive syndrome, but not only limited to concussions but all types of brain injuries (4).
- Second impact syndrome: experience of a second head injury before complete recovery from initial injury resulting in diffuse cerebral edema (5).
- Post concussive syndrome: physical, cognitive, behavioral and/or emotional symptoms that occur after experience of a mild traumatic brain injury (6). Symptoms persist beyond the usual recovery period after concussion (7).

- Post traumatic encephalopathy/ Chronic traumatic encephalopathy: progressive neurological deterioration caused by repetitive brain trauma (8).

EPIDEMIOLOGY/ PREDISPOSITION FOR LONG TERM SEQUELAE:

Mild TBI is the most common type of traumatic brain injury in the United States accounting for 75% of all traumatic brain injuries. Long term sequelae can also happen after moderate or severe injuries but appear more often in mild TBI.

Women seem to suffer more often from post concussive syndrome than men. There are several theories trying to explain this phenomenon, which include psychosocial factors, differences in symptom reporting, hormonal influences, and the use of ICD-10 rather than DSM IV criteria in the diagnosis. Also, incidences seem to increase with age and risks are higher if the patient suffered from multiple brain injuries. A protecting factor seems to be younger age, where increased neuroplasticity appears to have a positive influence on the outcome of traumatic brain injuries (6). Other sources additionally mention pre-injury, peri-injury and post injury factors which may increase the risk of post concussive syndrome occurrence. Pre-injury factors involve female gender, adolescent or higher age, psychiatric history and substance use, peri-injury factors contain mechanism of injury and MRI factors like number of visible contusions and shear foci and post injury factors include presence of PTSD, anxiety, depression and migraines (9). A study from Wäljas et al. containing a sample size of 126 mTBI patients showed an incidence of PCS of 59% after one month and 38% after one year (10).

Second impact syndrome (SIS) is an extremely rare and controversially discussed topic, which occurs in athletic children and adolescents (11). Mostly affected are young male athletes from age 13 till 24, playing contact sports like American Football, boxing and hockey (12).

Chronic traumatic encephalopathy is also mostly reported in athletes, especially American Football players, boxers, and military veterans.

Genetic factors influencing the pathophysiology of CTE are not yet clearly defined, even though ApoE4 carriers seem to be generally more at risk to suffer from severe outcomes after TBI (13). This apolipoprotein E e4 allele is thought to be involved in the inhibition of neuronal growth after brain injury. Furthermore, psychosocial factors and age may play a role (14). This ApoE4 gene is also associated with amyloid beta deposition in Alzheimer dementia (15). ApoE3 on the other hand might be a factor of neuroprotection (16). Falcon et al. suggest that co-factors which are needed for the assembly of tau protein, cross the blood brain barrier

after head trauma, therefore making individuals with higher levels of co-factors more susceptible to CTE (17).

LITERATURE SEARCH STRATEGY

For this research the database PubMed was searched for the following key words: post concussive syndrome, second impact syndrome, chronic traumatic encephalopathy/post traumatic encephalopathy, mild head injury, long term outcome of mild head injury, neurobehavioral sequelae. In total, the search for the aforementioned keywords yielded 12.634 results of which 1319 were for post concussive syndrome, 2029 for second impact syndrome, 6862 for mild head injury, 462 for long term outcome after TBI and 961 for chronic traumatic encephalopathy as well as 1001 for post traumatic encephalopathy. Criteria were publication dates not older than 10 years and availability of full text. On average, the first 5 pages of results were red and finally, 144 sources were included in this thesis, of which all articles were accessible either for free or with the Vilnius University VPN. In addition to that, more recent articles (written in last 5 years) were preferred as source to represent the newest research findings. This thesis contains only information from English sources. Neglected were all articles with a publication date less recent than 10 years, except for primary sources.

CLINICAL PRESENTATION

POSTCONCUSSIVE SYNDROME:

Post-concussive symptoms are transient in most cases and subside within 10 to 14 days after mild traumatic brain injury. There is however a subgroup which is called post-concussive syndrome (persistent post-concussive symptoms), which according to the DSM-IV occurs when symptoms persist for longer than three months (18). While transient post concussive symptoms are followed by full recovery, the persistent syndrome seems to have lasting effects on cognition, memory and learning and executive function (6). There is evidence, that in some cases, symptoms may last for over 6 months and some studies report that 5% of patients with initial mild traumatic brain injury are still complaining of symptoms after 12 months (10). A figurative time scale of the mentioned post-concussive symptoms can be seen in figure 1 (19).

Figure 1: Time scale and ethiology of post-concussive syndrome after mTBI (19)

The presenting symptoms can be of various types. In the research there can be found physical, behavioural, and emotional types of symptoms. Physical symptoms include headache, fatigue, vision and balance disturbances, dizziness and insomnia. (6) Other sources on the other hand split up the symptoms after concussion into vestibular, sensory, cognitive, and emotional groups. Cognitive symptoms here include forgetfulness, difficulty concentrating, attention and memory problems. Emotional problems include fatigue, insomnia, irritability, and depression. Examples for vestibular symptoms include imbalance, nausea and dizziness, while sensory symptoms include blurred vision, migraines, tinnitus and photo or phonophobia. (7)

SECOND IMPACT SYNDROME:

The outcome of this condition is most often poor and ranges from permanent disability to death. Older individuals above 19 years seem to have a better prognosis (12). Typical concussion symptoms of varying severity may be present after the first traumatic injury, like severe headache, nausea or vomiting, retrograde amnesia, dizziness, confusion, fatigue, vision, motor or sensory disturbances, poor coordination, irritability, or loss of consciousness, followed by collapse and subsequent coma after the second injury (5,20).

CHRONIC TRAUMATIC ENCEPHALOPATHY:

Symptoms include behavioural disturbances such as aggression and impulsivity, mood disturbances like anxiety, depression or mania and cognitive impairments like poor attention, language deficits, dementia, executive impairment, and memory deficits. There can also be motor deficits like ataxia and parkinsonism (13). The clinical presentation depends on the stage of disease progression. According to McKee, stage 1 shows mostly asymptomatic patients, who might complain of a mild short term memory deficit, mild aggression, or

depressive symptoms. Stage 2 can show more pronounced mood and behavioural symptoms. Cognitive deficits start with stage 3, while stage 4 presents with language and motor deficits, as well as psychotic symptoms (8). According to Stern et al. there are two main subtypes of CTE. The first one presents initially with affective changes while the second one involves more cognitive impairment (21). Gardner et al. on the other hand divided clinical symptoms into a classic and modern subtype. Classic symptoms include mainly motor symptoms like dysarthria, movement difficulties and later memory deficits, while modern type is mainly made up out of neuropsychiatric symptoms and later cognitive deficits (22). These two different symptoms can be explained by the classic type being reported in older publications and therefore mainly in boxers and the modern type being reported mostly after 2005 and therefore mostly in American Football players, consequently involving a different mechanism of injury (23).

MECHANISMS AND PATHOLOGY

TRAUMATIC BRAIN INJURY:

There are multiple pathomechanisms, which are thought to play a role in the development of acute and chronic changes occurring after traumatic brain injury. (24) These include:

1. Excitotoxicity for neurons and oligodendrocytes through activation of glutamate receptors,
2. Oxidative stress by generation of reactive oxygen and reactive nitrogen, which lead to irreversible neuronal membrane damage and subsequent secondary injury mechanisms and therefore dysfunction and cell death.
3. Delayed and prolonged apoptosis of neuronal or myelin producing cells as potential mechanism for the progressive nature of TBI (25), (24).
4. Inflammatory processes are an important secondary injury mechanism,with an increased activation of microglia and recruitment of macrophages into injured tissue and subsequently increased synthesis of proinflammatory and therefore potentially neurotoxic chemokines and cytokines (26–30). Inflammasome activation might also play a factor (31,32). Newer studies found that some inflammatory cells might be both neurodegenerative and reparative (33–35). Consequently, there are different phenotypes of distinct microglia/macrophage subsets, where M1 is proinflammatory and has cytotoxic properties, while M2 has anti-inflammatory and therefore progenerative & immunoregulatory functions (36,37).
5. White matter injury including diffuse axonal injury is another important mechanism of traumatic brain injury. The degree of axonal injury seems to be severity dependant (38).
6. Demyelination due to axonal damage or death of myelinating cells (24).

7. Moderate reductions in chronic cerebral blood flow which could aggravate inflammatory or excitotoxic processes (24).

POSTCONCUSSIVE SYNDROME:

Concussion according to the Zurich guidelines includes a combination of metabolic (39), physiologic (40) and microstructural (41) injuries to the brain. It is proposed that acceleration and deceleration forces cause shearing of neural and vascular structures of the brain (42) with sudden neuronal depolarization and subsequent transmission failure (43,44). In addition to that, psychogenic factors also play a role in developing a post-concussive syndrome.

Some sources believe that PCS is caused by damage to the autonomic nervous system. This affects the parasympathetic and sympathetic nervous system and can therefore be associated with depressive symptoms. It also affects cerebral blood flow, blood pressure and heart rate and therefore causing dizziness, headache, confusion and concentration problems (6)(45). The presence of reduced heart rate variability can be used to assess autonomic dysfunction, which is thought to represent an uncoupling between the autonomic centres of the brain and cardiovascular system (46). Studies discovered, that patients with mild traumatic brain injury were unable to switch from parasympathetic to sympathetic control in time when exercising, as they showed lower heart rates (47) and blood pressure (48) during exercise and standing up causing them to feel dizziness.

SECOND IMPACT SYNDROME:

Second impact syndrome per definition are two mild head injuries in close timely proximity to each other. The main proposed mechanism is the loss of autoregulation inside the brain after a first traumatic brain injury.

After a primary trauma, the brains autoregulatory mechanisms jump in and prevent from massive swelling by limiting cerebral blood flow which leads to the accumulation of lactate and therefore intracellular acidosis (49). This means that the brain is in a vulnerable state, without the ability to autoregulate (50), with reduced blood flow, altered metabolism, decreased protein synthesis and reduced oxidative capacity (51). This loss of autoregulation increases the risk of having deteriorated outcomes like hyperemic brain swelling, increased intracranial pressure and therefore brain herniation, if another injury occurred before the metabolic homeostasis of the brain is restored (39). This vulnerable state can last for up to ten days, which makes second impacts during that time span most dangerous (52). The closer

together the impacts are in time, the higher severity of cerebral pathology and symptoms can be expected (53).

The diffuse brain edema, also termed “malignant brain edema” can lead to compression of parenchyma and vasculature causing injury (11) as well as the mentioned catastrophic deterioration like brain herniation (54).

It is proposed that hyperemia leads to vascular congestion, which then leads to cerebral edema. Vascular congestion is further exacerbated by a dysfunctional trigeminal system which can affect parasympathetic activity and contributes to vasodilation. This leads to increased intracranial pressure and brain injury (11). Additionally subdural hematoma were found in most cases of SIS in a recent review (55).

CHRONIC TRAUMATIC ENCEPHALOPATHY:

Chronic traumatic encephalopathy results of either severe or repetitive mild traumatic brain injuries. Acceleration and deceleration forces seem to be important in the mechanism of TBI. Lateral (side to side) injuries result in more injury, than sagittal (front to back) forces.

CTE is considered a tauopathy because of the accumulation of tau protein and neurofibrillary tangles. The distribution pattern of tau can be considered as pathognomonic. It accumulates in neurons and glia with perivascular accentuation and involvement of the depths of sulci in neocortical grey matter. This perivascular accumulation of tau could be explained by a loss of the integrity of the blood brain barrier caused by axonal injury and micro-hemorrhage and subsequent release of neurotoxins (15,56).

Brains of affected individuals also show atrophy of the mamillary bodies, a mild ventricular enlargement (especially lateral and third), pallor of substantia nigra and thinning of the corpus callosum (15). There is also a general reduction of brain mass probably caused by the atrophy of the frontal, temporal and parietal lobe, scarring as well as neuronal loss of the cerebellar tonsils and cavum septum pellucidum with fenestrations (57). An exemplary MRI image of an enlarged cavum septi pellucidi can be seen in figure 2. This phenomenon with or without fenestrations is normally onle seen in newborns and its presence in adults could be explained by a fluid wave inside the lateral ventricles, which puts shearing forces on the septum (58).

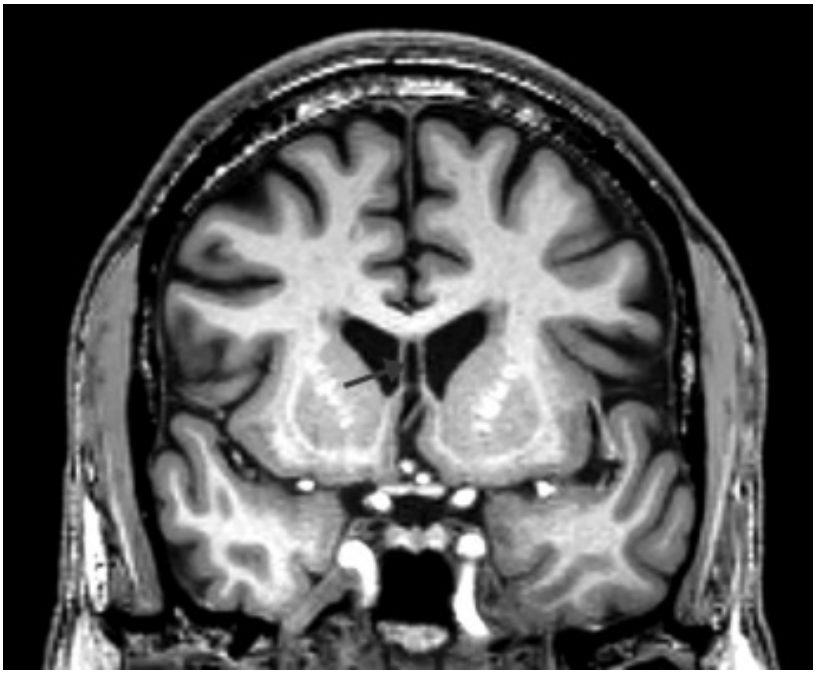

Figure 2: Cavum septi pellucidi on coronal plane of T1-weighted MRI of symptomatic, former professional football player, marked by an arrow (59).

One of the main histological signs is an accumulation of hyperphosphorylated TDP-43. This is the (TAR) DNA-binding protein 43. It's translocation from the nucleus to the cytoplasm is considered as a sign for neurodegenerative conditions such as Amyotrophic Lateral Sclerosis or frontotemporal lobar dementia. Neuronal loss, axonal degeneration and white matter degradation are further signs (15). A summary of the main pathological findings can be seen in figure 3.

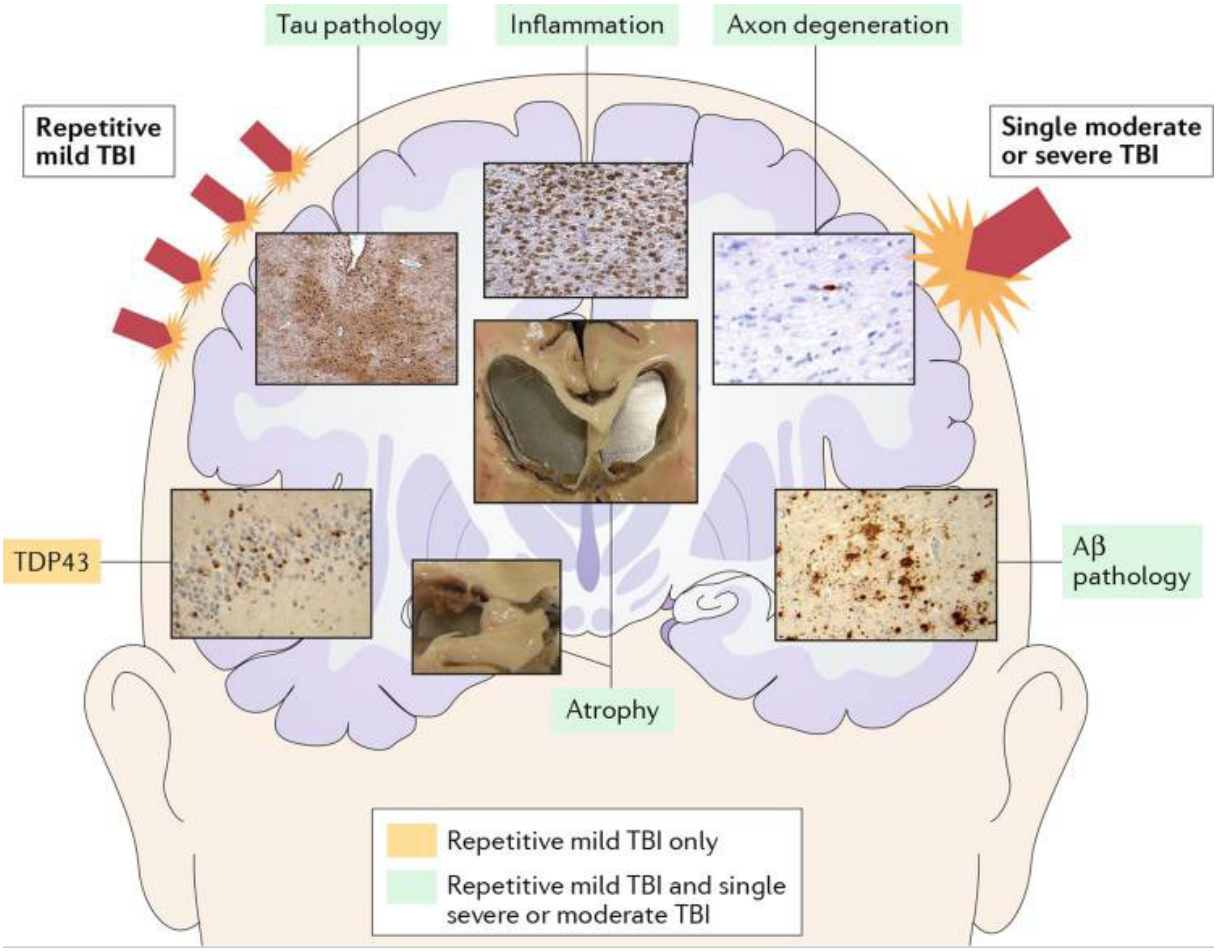

Figure 3: picture of the neuropathologies which are thought to be associated with neurodegeneration after traumatic brain injury (60)

There are four pathological stages:

- Stage 1: grossly normal brain with tau protein accumulation, neurofibrillary tangles, and neurites
- Stage 2: enlargement of ventricles, cavum septum pellucidum defects and multiple foci of accumulated tau protein
- Stage 3: brain weight loss with mild frontal and temporal lobe atrophy and dilation of the ventricles
- Stage 4: more dramatic reduction of brain weight, profound atrophy, septal defects and widespread accumulation of tau (8).

There are multiple theories trying to explain the pathologic accumulation of tau. One of them is based on evidence that reactive gliosis and redistribution of aquaporin 4 molecules lead to a disruption of the clearance of cerebrospinal fluid of interstitial beta-amyloid through the glymphatic system (brains lymphatic system) (61,62).

DIAGNOSIS

TRAUMATIC BRAIN INJURY:

In general, a detailed history should always be obtained and a thorough neurological examination should be conducted, including the examination of cranial nerves, peripheral reflexes and motor, balance and sensory function alongside a cognitive evaluation (63). There are often problems and limitations in the clinical diagnosis of long term sequelae after mild brain trauma due to the subjective description of symptoms and comorbidities or other factors that could influence or provoke symptoms, like normal aging, substance abuse or developmental environment (64).

For neuroimaging, structural MRI is the most commonly used modality for subacute to chronic traumatic brain injury (65,66) because it is able to identify characteristic injuries like white matter and axonal injury and brain atrophy. Other new possibilities in neuroimaging include susceptibility weighted imaging which is very sensitive in detecting hemorrhagic lesions, diffusion tensor imaging which can determine axonal integrity, MR spectroscopy and PET which are able to assess the brains metabolism and functional MRI to assess the brain's function (67).

Oxidative stress markers include carbonylated proteins, lipoperoxidases, reactive oxygen species and reactive nitrogen species as well as decreased antioxidant defense enzymes (68,69).

Inflammatory markers seen in traumatic brain injuries may include elevated levels of IL-1 in late stages (70) as well as elevated IL-1ß, TNF a, IL-6 and transforming growth factor (71,72)

POST CONCUSSIVE SYNDROME:

At this moment, there are two clinical criteria available to diagnose post concussive syndrome. This includes the commonly used ICD-10 (international classification of Diseases, 10th Revision) and the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders) (6). Both diagnostic criteria are similar in that they include three or more of the following symptoms: headache, dizziness, fatigue, irritability, insomnia, concentration or memory difficulty. One of the key differences is that DSM criteria additionally require neuropsychological evaluation of quantified cognitive assessment in addition to the symptoms occurring for at least 3 months, while the ICD-10 criteria require a symptom duration of 4 weeks (19). The DSM-IV diagnostic criteria seem to be more strict as studies found a

prevalence of PCS, 3 months after mTBI of 64% when using ICD-10 criteria, while the prevalence was only around 11% when using DSM-IV (73,74).

There are different self-reports used in the diagnosis of post concussive syndrome. The Rivermead post-concussion symptoms questionnaire (RPQ) is one of them. It is a self-test, which contains questions about common PCS symptoms like for example headaches, dizziness, mood disturbances and vision problems. (75)

It is important to differentiate PCS from pre-accidental conditions like migraine headaches, depression or chronic pain as well as other injuries like cervical injury (76).To differentiate post concussive symptoms from depression, exercise testing can be used, as concussion symptoms usually worsen with exercise (77) while the opposite should occur in depression (78). For the differentiation of cervical injuries, physical examination and imaging can be used.

There is growing evidence from neuroimaging and neurophysiological studies that indicates that prolonged symptoms are caused by occult brain dysfunction. (79,80) Problems are especially, that there is no consensus on regular follow ups after the acute period and what imaging techniques and biomarkers should be evaluated at what time. (7) Three imaging modalities discussed in multiple studies were evaluated in a review article by Biagianti et al. from 2020:

1. Resting state functional MRI (rsfMRI): Messé et al. performed a study where subjects underwent rsfMRI and graph theory examinations at subacute (8-21 days) and late phases (at 6 months). Persistent PCS was diagnosed at 6 months in 17 patients according to DSM-IV criteria. All mTBI patients showed increased connectivity in their limbic system. Persistent PCS patients additionally showed unique early thalamic and temporal lobe changes during subacute phase and decreased graph properties in frontal regions at the late phase. Other than in the H-MR spectroscopy study by Henry et al., objective changes correlated with reported symptoms (81).

Sours et al. performed a study of mTBI patients receiving rsfMRI and resting state perfusion scan using PASL technique at acute (1 week), subacute (1 month) and chronic phase (6 months). According to self-reported symptoms, 12 of 28 were categorized as PCS. Functional connectivity and cerebral blood flow were assessed. Results showed that all mTBI patients showed alterations in network perfusion in the chronic stage while PCS patients showed these signs in all three stages (82).

2. Diffusion weighted imaging (DWI): Patients were evaluated by DWI at subacute phase and late phase. PCS was detected by ICD-10 criteria in 22 of 53 mTBI patients. Impairments

in white matter fiber bundles were detected in all patients with mTBI. Patients with PCS showed longer persisting, greater and wider impairments than patients without PCS (83).

3. H-MR spectroscopy Imaging (HMRSI): The effect of mild traumatic brain injury on the metabolism of the brain were evaluated. Therefore, patients were evaluated during the acute (1-6 days) and chronic phase (at 6 months). Symptoms were assessed by Post concussion symptom scale, which consists of a 22 item self-report. Interestingly, subjective symptoms in the chronic phase were similar in both groups, as the affected group reported of clinical recovery. Objective analyses on the other hand painted a different picture as they still displayed some metabolic disruptions. Some disrupted metabolites normalized after the acute phase, while other cortical metabolic disruptions which were not present in the acute phase emerged over time and persisted during the chronic stage (84).

George et al. performed a similar study. They evaluated patients with post-concussion symptoms questionnaire (RPQ)(75) to assess severity of PCS and automated neuropsychological assessment metrics (ANAM)(85) to assess cognitive performance. The results showed decreased choline-to-creatinine ratio in mTBI patients in thalamus and centrum semiovale at late subacute phase. There were no correlations between severity of PCS and neurometabolic markers (86).

Summarizing the main findings in the review article of Biagianti (7), it can be said that in the studies by Messé and Sours et al. (81–83,87), patients with persistent PCS can show damage to structural integrity and signs of disrupted network communication or metabolism in acute and subacute phases. According to Biagianti, brain dysfunction can be categorized into quantitative (biomarkers or brain dysfunction in both groups, but higher quantity in PCS) or qualitative (unique biomarkers or brain dysfunction in PCS which is not visible in healthy control group).

Henry et al. showed that brain dysfunction can also be absent in acute and subacute phase and can only emerge in chronic phase. (84)

Recovery can be different. Some patients show compensatory reorganization with normalization and complete recovery, while in other patients, impairments may linger and contribute to the pathology of persistent PCS. Biomarkers found in the aforementioned studies include decreased fractional anisotropy values in association, commissural and projection white matter fibre tracts (83), lower graph properties in bilateral frontal gyri (81), greater perfusion in TPN nodes compared to DMN (87), reduced strength of DMN

connectivity (82), decreased thalamic functional capacity (88) and decreased connectivity in posterior regions of several resting state networks (89).

Henry et al. (84), George et al. (86) and Wäljäs et al. (10) studies found no association between PCS severity and appearance of biomarkers.

Difficulties in the appropriate diagnosis of PCS might have its origin in the unavailability of high-level neuroimaging protocols in clinical practice, therefore reliance on gross measures like CT scans, which often are not specific enough to show occult brain dysfunction or reliance of self-report rather than objective findings. Figure 4 shows some examples of head imaging with MRI sequences after concussion, where head CT was performed before and found to be normal. Consequently, post-concussive symptoms are often associated with as psychosocial factors by clinicians and treated with psychiatric medications like analgesics or anti-depressants. As a possible solution, repeated assessments for those where symptoms persist beyond acute period and do not have expected recovery, low impact and low cost rsfMRI can be applied as well as the RPQ (7).

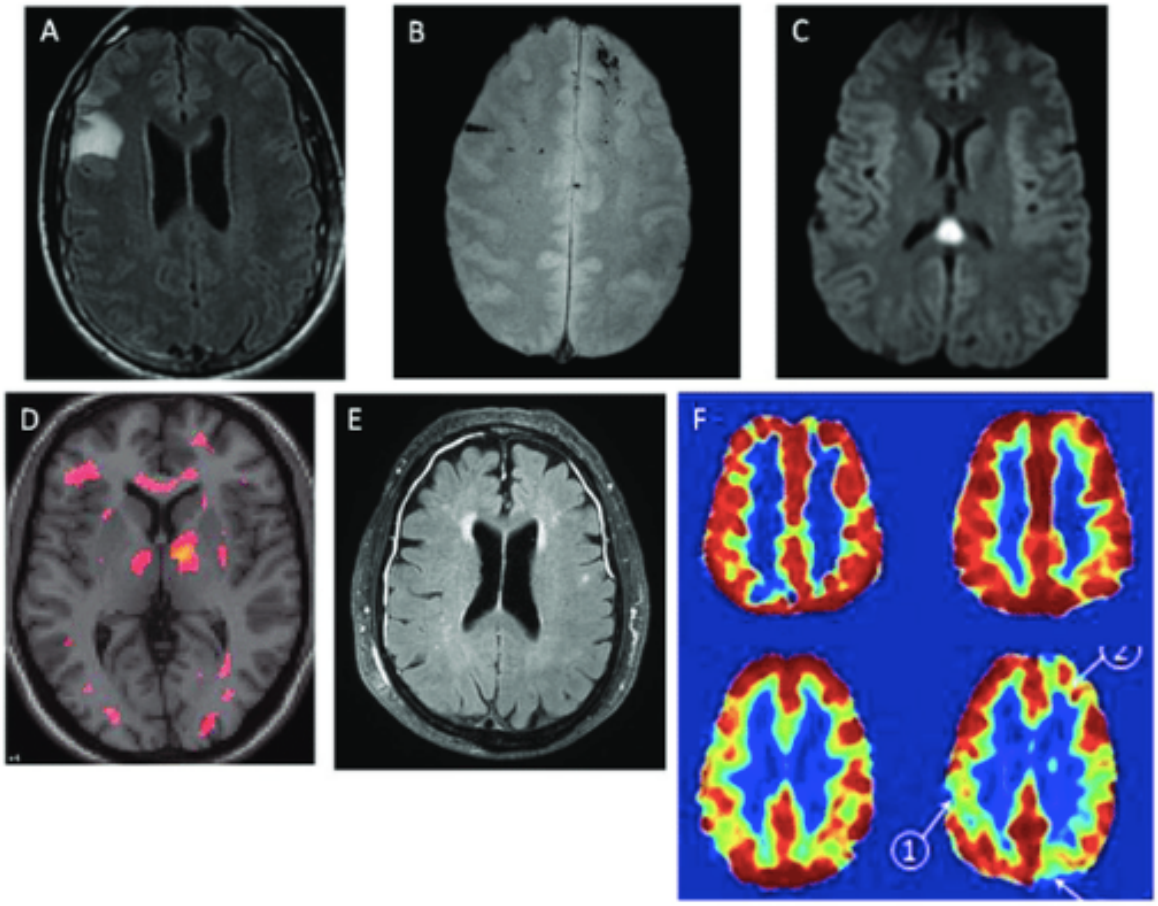

Figure 4: MRI of post-concussive symptoms after mTBI. In each case, cranial CT was normal and MRI was obtained within 48 h on injury. (A) Right frontal non-hemorrhagic contusion, on FLAIR. (B) Linear microhemorrhages in left and right frontal lobes, on T2*

image. (C) Diffuse axonal injury lesion in splenium of corpus callosum, with restricted diffusion on DWI image. (D) Diffuse axonal injury, with multifocal lesions on diffusion tensor imaging (DTI). (E) Traumatic meningeal enhancement of subdural effusions, on contrast FLAIR image. (F) Traumatic microvascular injury - Top row = healthy control; Bottom row = TBI patient - Left column: Cerebral Blood Flow, Right column: Cerebrovascular reactivity
(Credit for figures: Figures A, B, C, E: Larry Latour, PhD, NINDS/NIH; D: Carlos Marquez de la Plata, PhD, University of Texas at Dallas; F: Franck Amyot, PhD, Uniformed Services University of the Health Sciences. (73))

SECOND IMPACT SYNDROME:

Radiological evaluation:

CT can be used to reveal diffuse cerebral edema with midline shift, which can be considered as the pathognomic sign of this condition. There might also be brain herniation in the most severe cases, mild to moderate subdural hematomas not large enough to cause midline shift, subarachnoidal hemorrhage and ischemic stroke (12).
MRI with T2 and diffusion weighted imaging are even more sensitive for the described subtle changes but takes longer and is therefore not advised in emergency situations. Diffuse axonal injury can be seen as diffuse high-signal intensity specks within the white matter.

In a case described by Weinstein et al., the patient showed normal head CT results after the first impact and subtle changes like diffuse brain edema and thalamic injury only became visible after the second impact, when the patient already was in a very severe condition. The corresponding images are shown in figure 5.

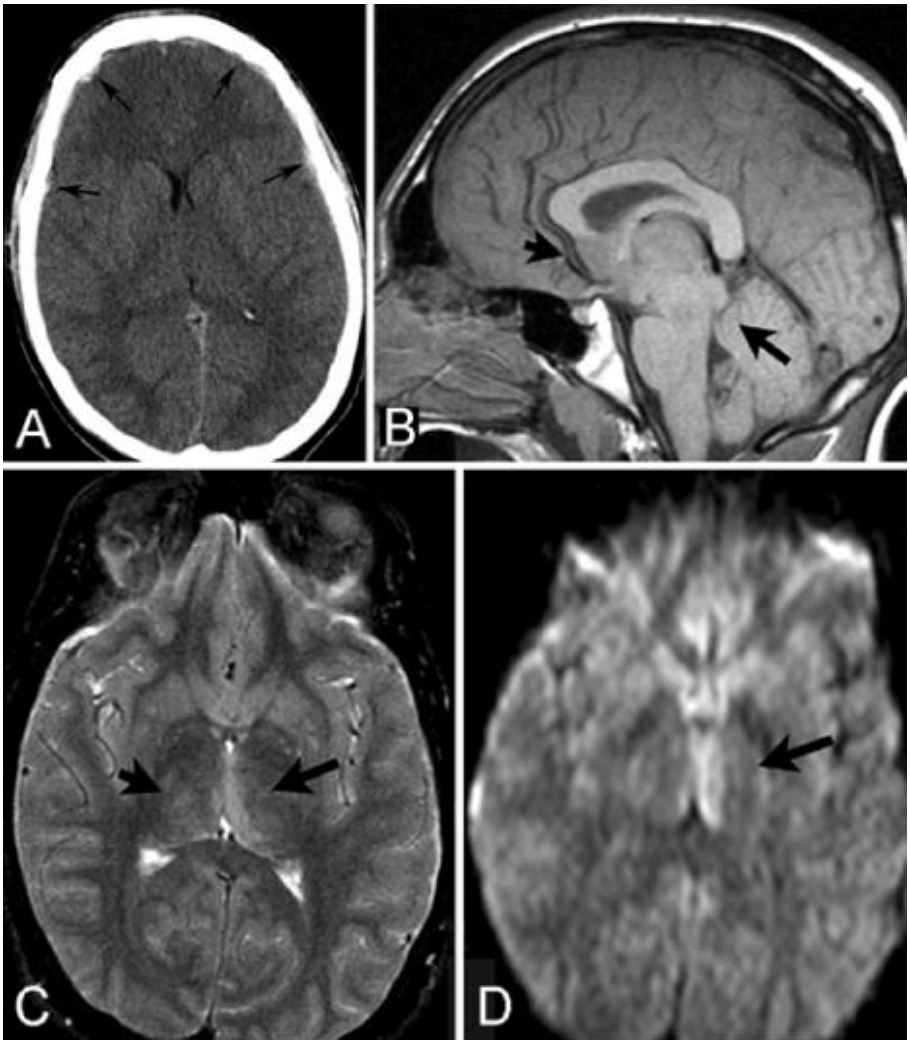

Figure 5: Picture from case in study by Weinstein et al. CT and MRI pictures were taken after second impact. A: head CT with arrows pointing to thin bilateral subdural hematomas. B: Sagittal T1 brain MR image with arrows pointing to downward descent of midline structures. C& D: Axial T2 MR image, arrows pointing to thalamic injury. Restricted diffusion was proven by calculation of apparent diffusion coefficient. (90)

N-acetylaspartate is a marker of high metabolism and is thought to be a possible marker for assessing concussion (91,92).

CHRONIC TRAUMATIC ENCEPHALOPATHY:

In 2014, there was a clinical classification proposed, which used the term traumatic encephalopathy syndrome (TES) instead of chronic traumatic encephalopathy. Those criteria allowed for a diagnosis in vivo, contrary to the CTE which can only be diagnosed by neuropathologic abnormalities post-mortem (67). The proposed diagnostic criteria according to Montenigro et al. (23) are classified into probable, possible and unlikely. Criteria include:

- history of TBI (mild, moderate/severe or sub concussive)
- source of exposure (contact sports, military service etc.)
- no other neurological disorder
- features present for over 12 months
- at least one clinical core feature (cognitive, behavioural or mood symptoms)
- at least two supportive features (impulsivity, anxiety, apathy, paranoia, suicidality, headache, motor signs, decline, delayed onset).

There are 4 different diagnostic subtypes:

1. behavioural/mood variant (behavioural or mood core features without cognitive)
2. cognitive variant (without behavioural or mood features)
3. mixed variant (cognitive and behavioural or mood features)
4. dementia (progressive cognitive with or without behavioural or mood features)

The biomarkers for the diagnosis include:

- septum pellucidum or fenestrations (neuroimaging)
- normal beta amyloid CSF level (diminished levels would indicate Alzheimer disease)
- elevated CSF p-tau/tau ratio
- negative amyloid and positive tau imaging (PET imaging with ligands that selectively bind to p-tau)
- cortical thinning and atrophy (MRI or CT) (23)

MANAGEMENT

MILD TRAUMATIC BRAIN INJURY:

In addition to initial stabilization in emergency situations, observation, analgesics and antiemetics as first measures, there are multiple studies investigating the use of other medications and treatment modalities for long term sequelae after mild traumatic brain injury. There are multiple experimental treatment possibilities, of which a few are mentioned in the following paragraph. However, most are of low level of evidence and would need further research and trials in order to establish a standard multidisciplinary management for those kind of patients.

The injury mechanism caused by oxidative stress can be improved by restoring oxidant and antioxidant balance (93–95) for example with selective poly (ADP ribose) polymerase 1 inhibition which in turn decreases generation of ROS and proinflammatory cytokines (96).

There are multiple proposed mechanisms to decrease excitotoxicity for example by inhibition of specific glutamatergic receptors which results in protection in terms of cell death(24)(97–99). Another protective treatment could be directed towards NMDA or AMPA receptor activation (100–102)(103). Other studies evaluated the use of experimental IL-1ß receptor blockers (104–110) or progesterone or anti-inflammatory steroids (111).
Another theory is therapeutic hypothermia. It is thought, that early cooling and temperature management may reduce levels of TNF alpha and IL1ß levels as well as an abnormal activation of inflammasome (112–117).
Reduced blood flow to the brain could be treated with Nitric Oxide to dilate vessels and restore an adequate perfusion of brain vessels.
A recently suggested therapy option is hyperbaric oxygen therapy (HBOT), which was traditionally used after diving accidents or in the case of difficult wound healing, but now also seems to be a promising option in this field of medicine, where multiple studies showed definite improvements in cognitive functions after HBOT (118–120). Proposed mechanisms of action of HBOT are for example oxygenation of hypoxic tissue (121), restoration of mitochondrial function (122), increased brain metabolism (123) and angiogenesis for restoration of cerebral blood flow and axonal regeneration (124).
The most important and reliable management option up to today remains prevention. Education in sports and military training are necessary to prevent the occurrence and recurrence of head injuries (13).

POSTCONCUSSIVE SYNDROME:

One of the most important management strategies concerning PCS are cognitive training, cognitive behavioral therapy and occupational therapy (125–127).
Other studies additionally mention the value of low level (aerobic) exercise rehabilitation (63,128,129) in combination with rest (130).
Experimental possibilities include sertraline, where some studies showed it being effective in preventing post TBI depression when administered early after the injury (79), repetitive transcranial magnetic stimulation, vestibular and vision rehabilitation therapy and anti-migraine medications for headaches (19). The question when a return to sports is advisable is an important topic to prevent long term physical limitations as well as severe syndromes like the mentioned second impact syndrome. A proposed algorithm for this decision can be seen in figure 6.

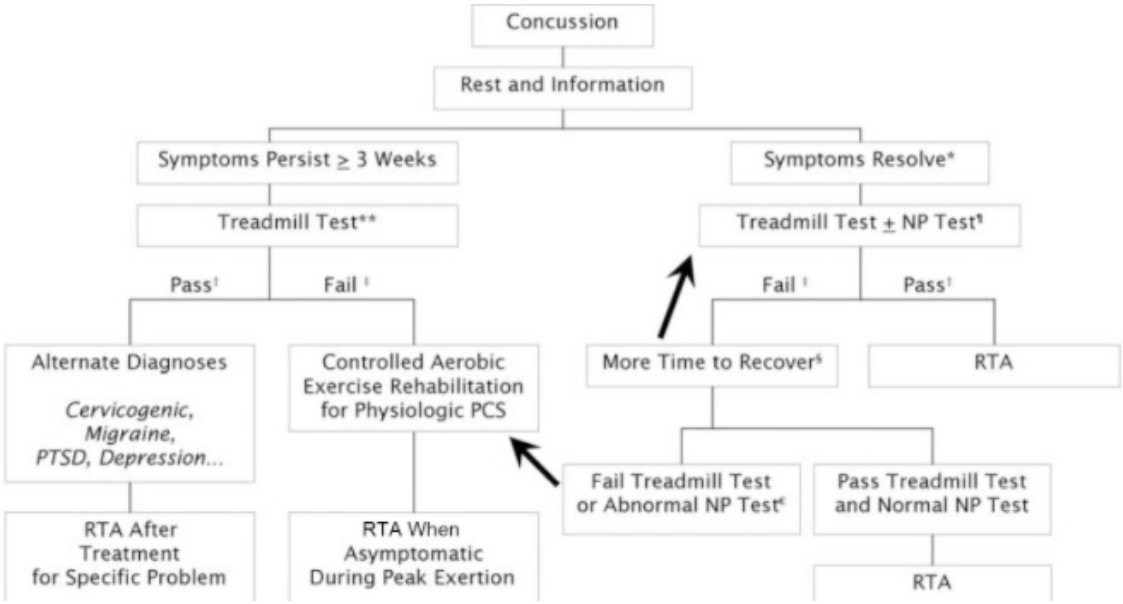

Figure 6: Algorithm of returning to activity (RTA) after concussion (129). (NP= neuropsychological)

SECOND IMPACT SYNDROME:

The main goal is to decrease the intracranial pressure and reduce the subsequent brain edema. Therefore, mild hyperventilation, reverse Trendelenburg positioning, IV mannitol or hypertonic saline is suggested. Emergent surgical possibilities include an external ventricular drain or bifrontal decompressive craniectomy. For neuroprotection, the induction of a pentobarbital coma is advised (90,131). In case of circulatory failure, standard resuscitation methods are advised like airway management, restoring a stable circulation and neurosurgery consult.

As also mentioned in the other paragraphs, prevention is one of the best possibilities in such cases, as there are yet only limited treatment options available (11).

CHRONIC TRAUMATIC ENCEPHALOPATHY:

Prevention of multiple injuries is the main management possibility in this neurodegenerative disease. Therefore after concussion it should be waited for at least one month before returning to sports (58). Some experimental studies mention co-factors as a possible target for therapy (17) and anti-inflammatory agents like minocycline with N-acetylcysteine (anti-oxidant) in acute and subacute post TBI (132,133).

Monoclonal antibody therapy or tau lowering oligonucleotides against pathogenic cis-tau protein are also a promising, but still evolving and experimental strategy in the management of CTE (134). As it is problematic for antibodies to cross the blood brain barrier, unilateral

focused ultrasound (FUS) has been discussed as a method to increase permeability of the barrier through producing transient openings in the tight junctions of endothelium (135). Microbubbles can be injected together with FUS to decrease side effects (136,137). Some studies discovered that the application of FUS even without added pharmaceuticals, as well as low intensity pulsed ultrasound (LIPUS) showed improvements in TBI and CTE patients (118,138,139).

Another experimental treatment option could be kinase inhibitors, which can inhibit the formation of neurofibrillary tangles by inhibiting the hyperphosphorylation of functional to pathogenic tau (134).

DISCUSSION

Despite grand amounts of existing research, these syndromes are hard to grasp because there are many contradictory findings and theories, as these phenomena are still rarely seen, and the spectrum of reported symptoms and clinical findings is quite broad. Consequently, clear definitions, predisposing factors, time span, diagnostic criteria and routine treatment possibilities are yet hard to define. Incidences seem to be higher among women and the main vulnerable group for all three described long-term sequelae are contact sport players and other persons exposed to multiple head injuries. Apo E3 seems to be a protective factor, while Apo E4 and higher amounts of co-factors for tau protein assembly are thought to be associated with higher incidences of those sequelae.

Post-concussive syndrome includes physical symptoms such as headache, fatigue, and vision problems, as well as cognitive and emotional deficits, which persist longer than typical post-concussive symptoms. A definite time scale is hard to find, but most sources describe a duration of at least 3 months. Basic pathophysiology seems to include damage to the autonomic nervous system and therefore dysregulation of the parasympathetic and sympathetic systems.

Second impact syndrome describes the occurrence of a second head injury during a vulnerable state of the brain before it could completely recover. During this time, auto-regulatory mechanisms of the brain often do not function properly and leave the brain with an altered blood flow and metabolism and therefore vulnerable to extensive damage if a second injury should occur. Patients often report post-concussive symptoms like headache, dizziness, and nausea after the first injury, followed by a collapse after the second injury with the presence of pathognomic diffuse malignant cerebral edema. Children are most vulnerable for this type of injury while individuals over 19 years seem to have a better prognosis.

Post traumatic encephalopathy, or chronic traumatic encephalopathy describes a progressive neurological deterioration with behaviour and mood disturbances such as aggression, dementia, and motor deficits. This long-term sequel is defined by a pathognomic accumulation of pathologic tau protein in neurons and glia with a perivascular accentuation and includes 4 different stages and 2 subtypes. The stages range from mild or asymptomatic in stage 1 over mood and behavioural symptoms (2) and cognitive deficits (3) to language and motor deficits in stage 4, while the subtypes include a modern (mainly neuropsychiatric and cognitive symptoms which are associated with American football players as the vulnerable group) and a classic subtype (mostly motor symptoms and associated with boxers)
Diagnosis of the mentioned sequelae involves specific modalities next to the usual gathering of anamnestic data, laboratory investigations, clinical evaluation and conventional imaging like CT and MRI. Specific laboratory biomarkers such as oxidative stress markers, inflammatory interleukins and N-acetylaspartate, and brain imaging like susceptibility weighted imaging, diffusion tensor imaging, MR spectroscopy, PET and functional MRI are much more specific than conventional diagnostic possibilities but are not available in most medical centres. Together with subjective varying symptom descriptions, only minor structural pathological signs and close to non-existent standards, makes this the definite diagnosis of those syndromes much more difficult.
For management options, there are multiple proposed experimental medical therapies like monoclonal antibodies, anti-depressants well as the appliance of transcranial brain stimulation, hyperbaric oxygen therapy or ultrasound, but the most effective seems to be prevention, next to rest, physical and psychological rehabilitation together with close observation by trained specialists and a prolonged time period until returning to sports/work.

CONCLUSIONS

Finding a definition and confirming the diagnosis of long-term sequelae after mild traumatic brain injury can be complicated. It is not clearly understood as to why most patients recover quickly within days, weeks, or months, and some people have poorer outcomes and long-term sequelae.
Finding uniform diagnostic criteria seems to be fairly difficult with conventional CT not being able to detect the subtle brain changes in those long-term sequelae by only showing gross brain anomalies and hemorrhages. MRI seems to be more specific and able to detect white matter and axonal injury together with brain atrophy, but yet more specific imaging techniques are needed to evaluate the full extent of brain pathology in such cases. Possibilities

here include susceptibility weighted imaging to detect minor hemorrhagic lesions, diffusion tensor imaging to determine axonal integrity, MR spectroscopy & PET to evaluate brain metabolism and functional MRI for brain function.

As there is no definite treatment method, prevention seems to be the key take home message as it is the only proven, effective measure for avoiding the previously mentioned long term sequelae. Therefore, ongoing educating activities should be encouraged, especially for members of the mentioned risk groups like young contact sport players and military personnel. These education programs could include safety measures during sports like protective gear and information about the typical procedure after obtaining a head injury like information about the "normal" time span and type of symptoms. A close collaboration with professional medical personnel should be encouraged, who could perform specific questionnaires, laboratory tests and brain imaging to evaluate the severity and persistence of symptoms and could therefore help in making an informed decision about when a return to sports might be safely possible.

REFERENCES

1. Kay T, Harrington DE, Adams R, Anderson T, Berrol S, Cicerone K, u. a. Definition of mild traumatic brain injury. J Head Trauma Rehabil. September 1993;8(3):86–7.
2. Ruff RM, Iverson GL, Barth JT, Bush SS, Broshek DK, the NAN Policy and Planning Committee. Recommendations for Diagnosing a Mild Traumatic Brain Injury: A National Academy of Neuropsychology Education Paper. Arch Clin Neuropsychol. 1. Februar 2009;24(1):3–10.
3. Carroll L.J., Cassidy J.D., Holm L., Kraus J., Coronado V.G. Methodological issues and research recommendations for mild traumatic brain injury: the WHO collaborating centre task force on mild traumatic brain injury. J Rehabil Med. 2004;43:113–25.
4. Riggio S, Wong M. Neurobehavioral sequelae of traumatic brain injury. Mt Sinai J Med J Transl Pers Med. April 2009;76(2):163–72.
5. May T, Foris LA, Donnally III CJ. Second Impact Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [zitiert 28. November 2021]. Verfügbar unter: http://www.ncbi.nlm.nih.gov/books/NBK448119/
6. Permenter CM, Fernández-de Thomas RJ, Sherman A l. Postconcussive Syndrome. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [zitiert 21. Oktober 2021]. Verfügbar unter: http://www.ncbi.nlm.nih.gov/books/NBK534786/
7. Biagianti B, Stocchetti N, Brambilla P, Van Vleet T. Brain dysfunction underlying prolonged post-concussive syndrome: A systematic review. J Affect Disord. Februar 2020;262:71–6.
8. McKee AC, Stein TD, Kiernan PT, Alvarez VE. The neuropathology of chronic traumatic encephalopathy. Brain Pathol Zurich Switz. Mai 2015;25(3):350–64.
9. Quinn DK, Mayer AR, Master CL, Fann JR. Prolonged Postconcussive Symptoms. Am J Psychiatry. Februar 2018;175(2):103–11.
10. Wäljas M, Iverson GL, Lange RT, Hakulinen U, Dastidar P, Huhtala H, u. a. A prospective biopsychosocial study of the persistent post-concussion symptoms following mild traumatic brain injury. J Neurotrauma. 15. April 2015;32(8):534–47.

11. Bey T, Ostick B. Second impact syndrome. West J Emerg Med. Februar 2009;10(1):6–10.
12. McLendon LA, Kralik SF, Grayson PA, Golomb MR. The Controversial Second Impact Syndrome: A Review of the Literature. Pediatr Neurol. September 2016;62:9–17.
13. Fesharaki-Zadeh A. Chronic Traumatic Encephalopathy: A Brief Overview. Front Neurol. 2019;10:713.
14. Inserra CJ, DeVrieze BW. Chronic Traumatic Encephalopathy. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2021 [zitiert 28. November 2021]. Verfügbar unter: http://www.ncbi.nlm.nih.gov/books/NBK470535/
15. Hay J, Johnson VE, Smith DH, Stewart W. Chronic Traumatic Encephalopathy: The Neuropathological Legacy of Traumatic Brain Injury. Annu Rev Pathol Mech Dis. 23. Mai 2016;11(1):21–45.
16. Omalu BI, DeKosky ST, Minster RL, Kamboh MI, Hamilton RL, Wecht CH. Chronic Traumatic Encephalopathy in a National Football League Player. Neurosurgery. 1. Juli 2005;57(1):128–34.
17. Falcon B, Zivanov J, Zhang W, Murzin AG, Garringer HJ, Vidal R, u. a. Novel tau filament fold in chronic traumatic encephalopathy encloses hydrophobic molecules. Nature. April 2019;568(7752):420–3.
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Edition. Am Psychiatr Assoc. 1994;
19. Hadanny A, Efrati S. Treatment of persistent post-concussion syndrome due to mild traumatic brain injury: current status and future directions. Expert Rev Neurother. 2. August 2016;16(8):875–87.
20. Knipe H, Ibrahim D. Second-impact syndrome. In: Radiopaedia.org [Internet]. Radiopaedia.org; 2017 [zitiert 4. März 2022]. Verfügbar unter: http://radiopaedia.org/articles/53228
21. Stern RA, Daneshvar DH, Baugh CM, Seichepine DR, Montenigro PH, Riley DO, u. a. Clinical presentation of chronic traumatic encephalopathy. Neurology. 24. September 2013;81(13):1122–9.
22. Gardner A, Iverson GL, McCrory P. Chronic traumatic encephalopathy in sport: a systematic review. Br J Sports Med. Januar 2014;48(2):84–90.
23. Montenigro PH, Baugh CM, Daneshvar DH, Mez J, Budson AE, Au R, u. a. Clinical subtypes of chronic traumatic encephalopathy: literature review and proposed research diagnostic criteria for traumatic encephalopathy syndrome. Alzheimers Res Ther. Oktober 2014;6(5–8):68.
24. Bramlett HM, Dietrich WD. Long-Term Consequences of Traumatic Brain Injury: Current Status of Potential Mechanisms of Injury and Neurological Outcomes. J Neurotrauma. Dezember 2015;32(23):1834–48.
25. Raghupathi R. Cell Death Mechanisms Following Traumatic Brain Injury. Brain Pathol. April 2004;14(2):215–22.
26. Acosta SA, Tajiri N, Shinozuka K, Ishikawa H, Grimmig B, Diamond D, u. a. Long-Term Upregulation of Inflammation and Suppression of Cell Proliferation in the Brain of Adult Rats Exposed to Traumatic Brain Injury Using the Controlled Cortical Impact Model. Christie B, Herausgeber. PLoS ONE. 3. Januar 2013;8(1):e53376.
27. Nonaka M, Chen X-H, Pierce JES, Leoni MJ, McINTOSH TK, Wolf JA, u. a. Prolonged Activation of NF-κB Following Traumatic Brain Injury in Rats. J Neurotrauma. November 1999;16(11):1023–34.
28. Gentleman SM, Leclercq PD, Moyes L, Graham DI, Smith C, Griffin WST, u. a. Long-term intracerebral inflammatory response after traumatic brain injury. Forensic Sci Int. Dezember 2004;146(2–3):97–104.
29. Loane DJ, Kumar A, Stoica BA, Cabatbat R, Faden AI. Progressive

Neurodegeneration After Experimental Brain Trauma: Association With Chronic Microglial Activation. J Neuropathol Exp Neurol. Januar 2014;73(1):14–29.
30. Rodriguez-Paez AC, Brunschwig JP, Bramlett HM. Light and electron microscopic assessment of progressive atrophy following moderate traumatic brain injury in the rat. Acta Neuropathol (Berl). Juni 2005;109(6):603–16.
31. de Rivero Vaccari JP, Lotocki G, Marcillo AE, Dietrich WD, Keane RW. A Molecular Platform in Neurons Regulates Inflammation after Spinal Cord Injury. J Neurosci. 26. März 2008;28(13):3404–14.
32. de Rivero Vaccari JP, Dietrich WD, Keane RW. Activation and Regulation of Cellular Inflammasomes: Gaps in Our Knowledge for Central Nervous System Injury. J Cereb Blood Flow Metab. März 2014;34(3):369–75.
33. Donnelly DJ, Gensel JC, Ankeny DP, van Rooijen N, Popovich PG. An efficient and reproducible method for quantifying macrophages in different experimental models of central nervous system pathology. J Neurosci Methods. Juni 2009;181(1):36–44.
34. Kigerl KA, Gensel JC, Ankeny DP, Alexander JK, Donnelly DJ, Popovich PG. Identification of Two Distinct Macrophage Subsets with Divergent Effects Causing either Neurotoxicity or Regeneration in the Injured Mouse Spinal Cord. J Neurosci. 28. Oktober 2009;29(43):13435–44.
35. Gensel JC, Kigerl KA, Mandrekar-Colucci SS, Gaudet AD, Popovich PG. Achieving CNS axon regeneration by manipulating convergent neuro-immune signaling. Cell Tissue Res. Juli 2012;349(1):201–13.
36. Hu X, Li P, Guo Y, Wang H, Leak RK, Chen S, u. a. Microglia/Macrophage Polarization Dynamics Reveal Novel Mechanism of Injury Expansion After Focal Cerebral Ischemia. Stroke. November 2012;43(11):3063–70.
37. Chhor V, Le Charpentier T, Lebon S, Oré M-V, Celador IL, Josserand J, u. a. Characterization of phenotype markers and neuronotoxic potential of polarised primary microglia in vitro. Brain Behav Immun. August 2013;32:70–85.
38. Povlishock JT, Christman CW. The Pathobiology of Traumatically Induced Axonal Injury in Animals and Humans: A Review of Current Thoughts. J Neurotrauma. August 1995;12(4):555–64.
39. Giza CC, Hovda DA. The Neurometabolic Cascade of Concussion. J Athl Train. September 2001;36(3):228–35.
40. McKeag DB, Kutcher JS. Concussion Consensus: Raising the Bar and Filling in the Gaps. Clin J Sport Med. September 2009;19(5):343–6.
41. Bazarian JJ. Preface. J Head Trauma Rehabil. Juli 2010;25(4):225–7.
42. Johnston KM, McCrory P, Mohtadi NG, Meeuwisse W. Evidence-Based Review of Sport-Related Concussion: Clinical Science: Clin J Sport Med. Juli 2001;11(3):150–9.
43. Shetter AG, Demakas JJ. The pathophysiology of concussion: a review. Adv Neurol. 1979;22:5–14.
44. Ward AA. The Physiology of Concussion. Neurosurgery. 1. Januar 1966;12(CN_suppl_1):95–111.
45. Leddy J, Baker JG, Haider MN, Hinds A, Willer B. A Physiological Approach to Prolonged Recovery From Sport-Related Concussion. J Athl Train. 1. März 2017;52(3):299–308.
46. Goldstein B, Toweill D, Lai S, Sonnenthal K, Kimberly B. Uncoupling of the autonomic and cardiovascular systems in acute brain injury. Am J Physiol-Regul Integr Comp Physiol. 1. Oktober 1998;275(4):R1287–92.
47. Hinds A, Leddy J, Freitas M, Willer B. The Effect of Exertion on Heart Rate and Rating of Perceived Exertion in Acutely Concussed Individuals. J Neurol Neurophysiol [Internet]. 2016 [zitiert 10. Dezember 2021];7(4). Verfügbar unter: https://www.omicsonline.org/open-access/the-effect-of-exertion-on-heart-rate-and-rating-of-

perceived-exertion-inacutely-concussed-individuals-2155-9562-1000388.php?aid=78314
48. Hilz MJ, DeFina PA, Anders S, Koehn J, Lang CJ, Pauli E, u. a. Frequency Analysis Unveils Cardiac Autonomic Dysfunction after Mild Traumatic Brain Injury. J Neurotrauma. September 2011;28(9):1727–38.
49. DeSalles AAF, Kontos HA, Ward JD, Marmarou A, Becker DP. Brain Tissue pH in Severely Head-injured Patients: A Report of Three Cases: Neurosurgery. Februar 1987;20(2):297–301.
50. Cantu RC. SECOND-IMPACT SYNDROME. Clin Sports Med. Januar 1998;17(1):37–44.
51. Maroon JC, Lovell MR, Norwig J, Podell K, Powell JW, Hartl R. Cerebral Concussion in Athletes: Evaluation and Neuropsychological Testing. Neurosurgery. 1. September 2000;47(3):659–72.
52. Kawamata T, Katayama Y, Hovda DA, Yoshino A, Becker DP. Administration of Excitatory Amino Acid Antagonists via Microdialysis Attenuates the Increase in Glucose Utilization Seen following Concussive Brain Injury. J Cereb Blood Flow Metab. Januar 1992;12(1):12–24.
53. Prins ML, Alexander D, Giza CC, Hovda DA. Repeated Mild Traumatic Brain Injury: Mechanisms of Cerebral Vulnerability. J Neurotrauma. Januar 2013;30(1):30–8.
54. McCrory P. Does Second Impact Syndrome Exist?: Clin J Sport Med. Juli 2001;11(3):144–9.
55. Thomas M, Haas TS, Doerer JJ, Hodges JS, Aicher BO, Garberich RF, u. a. Epidemiology of Sudden Death in Young, Competitive Athletes Due to Blunt Trauma. Pediatrics. 1. Juli 2011;128(1):e1–8.
56. Geddes JF, Vowles GH, Nicoll JAR, Révész T. Neuronal cytoskeletal changes are an early consequence of repetitive head injury. Acta Neuropathol (Berl). 6. August 1999;98(2):171–8.
57. Corsellis JAN, Bruton CJ, Freeman-Browne D. The aftermath of boxing. Psychol Med. August 1973;3(3):270–303.
58. McKee AC, Cantu RC, Nowinski CJ, Hedley-Whyte ET, Gavett BE, Budson AE, u. a. Chronic Traumatic Encephalopathy in Athletes: Progressive Tauopathy After Repetitive Head Injury. J Neuropathol Exp Neurol. Juli 2009;68(7):709–35.
59. Lin A, Charney M, Shenton ME, Koerte IK. Chronic traumatic encephalopathy: neuroimaging biomarkers. In: Handbook of Clinical Neurology [Internet]. Elsevier; 2018 [zitiert 6. Februar 2022]. S. 309–22. Verfügbar unter: https://linkinghub.elsevier.com/retrieve/pii/B978044463954700029X
60. Smith DH, Johnson VE, Trojanowski JQ, Stewart W. Chronic traumatic encephalopathy - confusion and controversies. Nat Rev Neurol. März 2019;15(3):179–83.
61. Iliff JJ, Nedergaard M. Is There a Cerebral Lymphatic System? Stroke [Internet]. Juni 2013 [zitiert 4. März 2022];44(6_suppl_1). Verfügbar unter: https://www.ahajournals.org/doi/10.1161/STROKEAHA.112.678698
62. Sharma R, Knipe H. Chronic traumatic encephalopathy. In: Radiopaedia.org [Internet]. Radiopaedia.org; 2015 [zitiert 4. März 2022]. Verfügbar unter: http://radiopaedia.org/articles/40778
63. McCrory P, Meeuwisse W, Aubry M, Cantu B, Dvorak J, Echemendia RJ, u. a. Consensus Statement on Concussion in Sport—the 4th International Conference on Concussion in Sport Held in Zurich, November 2012. Clin J Sport Med. März 2013;23(2):89–117.
64. Asken BM, Sullan MJ, Snyder AR, Houck ZM, Bryant VE, Hizel LP, u. a. Factors Influencing Clinical Correlates of Chronic Traumatic Encephalopathy (CTE): a Review. Neuropsychol Rev. Dezember 2016;26(4):340–63.
65. Wintermark M, Sanelli PC, Anzai Y, Tsiouris AJ, Whitlow CT, Druzgal TJ, u. a.

Imaging Evidence and Recommendations for Traumatic Brain Injury: Conventional Neuroimaging Techniques. J Am Coll Radiol. Februar 2015;12(2):e1–14.
66. Ventricular dilation, cortical atrophy, and neuropsychological outcome following traumatic brain injury. J Neuropsychiatry Clin Neurosci. Februar 1995;7(1):42–8.
67. Perrine K, Helcer J, Tsiouris AJ, Pisapia DJ, Stieg P. The Current Status of Research on Chronic Traumatic Encephalopathy. World Neurosurg. Juni 2017;102:533–44.
68. Hall ED, Wang JA, Miller DM. Relationship of nitric oxide synthase induction to peroxynitrite-mediated oxidative damage during the first week after experimental traumatic brain injury. Exp Neurol. Dezember 2012;238(2):176–82.
69. Rodriguez-Rodriguez A, Egea-Guerrero J, Murillo-Cabezas F, Carrillo-Vico A. Oxidative Stress in Traumatic Brain Injury. Curr Med Chem. 31. März 2014;21(10):1201–11.
70. McClain CJ, Cohen D, Ott L, Dinarello CA, Young B. Ventricular fluid interleukin-1 activity in patients with head injury. J Lab Clin Med. Juli 1987;110(1):48–54.
71. Morganti-Kossmann MC, Rancan M, Stahel PF, Kossmann T. Inflammatory response in acute traumatic brain injury: a double-edged sword: Curr Opin Crit Care. April 2002;8(2):101–5.
72. Ziebell JM, Morganti-Kossmann MC. Involvement of pro- and anti-inflammatory cytokines and chemokines in the pathophysiology of traumatic brain injury. Neurotherapeutics. Januar 2010;7(1):22–30.
73. Polinder S, Cnossen MC, Real RGL, Covic A, Gorbunova A, Voormolen DC, u. a. A Multidimensional Approach to Post-concussion Symptoms in Mild Traumatic Brain Injury. Front Neurol. 19. Dezember 2018;9:1113.
74. Boake C, McCauley SR, Levin HS, Pedroza C, Contant CF, Song JX, u. a. Diagnostic Criteria for Postconcussional Syndrome After Mild to Moderate Traumatic Brain Injury. J Neuropsychiatry Clin Neurosci. August 2005;17(3):350–6.
75. King NS, Crawford S, Wenden FJ, Moss NE, Wade DT. The Rivermead Post Concussion Symptoms Questionnaire: a measure of symptoms commonly experienced after head injury and its reliability. J Neurol. September 1995;242(9):587–92.
76. Kutcher JS, Eckner JT. At-Risk Populations in Sports-Related Concussion: Curr Sports Med Rep. Januar 2010;9(1):16–20.
77. McCrory P, Johnston K, Meeuwisse W, Aubry M, Cantu R, Dvorak J, u. a. Summary and Agreement Statement of the 2nd International Conference on Concussion in Sport, Prague 2004. Clin J Sport Med. März 2005;15(2):48–55.
78. Dimeo F. Benefits from aerobic exercise in patients with major depression: a pilot study. Br J Sports Med. 1. April 2001;35(2):114–7.
79. Mayer AR, Bellgowan PSF, Hanlon FM. Functional magnetic resonance imaging of mild traumatic brain injury. Neurosci Biobehav Rev. Februar 2015;49:8–18.
80. Rapp PE, Keyser DO, Albano A, Hernandez R, Gibson DB, Zambon RA, u. a. Traumatic Brain Injury Detection Using Electrophysiological Methods. Front Hum Neurosci [Internet]. 4. Februar 2015 [zitiert 30. November 2021];9. Verfügbar unter: http://journal.frontiersin.org/Article/10.3389/fnhum.2015.00011/abstract
81. Messé A, Caplain S, Pélégrini-Issac M, Blancho S, Lévy R, Aghakhani N, u. a. Specific and evolving resting-state network alterations in post-concussion syndrome following mild traumatic brain injury. PloS One. 2013;8(6):e65470.
82. Sours C, Chen H, Roys S, Zhuo J, Varshney A, Gullapalli RP. Investigation of Multiple Frequency Ranges Using Discrete Wavelet Decomposition of Resting-State Functional Connectivity in Mild Traumatic Brain Injury Patients. Brain Connect. September 2015;5(7):442–50.
83. Messé A, Caplain S, Pélégrini-Issac M, Blancho S, Montreuil M, Lévy R, u. a. Structural integrity and postconcussion syndrome in mild traumatic brain injury patients. Brain Imaging Behav. Juni 2012;6(2):283–92.

84. Henry LC, Tremblay S, Leclerc S, Khiat A, Boulanger Y, Ellemberg D, u. a. Metabolic changes in concussed American football players during the acute and chronic post-injury phases. BMC Neurol. Dezember 2011;11(1):105.
85. Kane R, Roebuckspencer T, Short P, Kabat M, Wilken J. Identifying and monitoring cognitive deficits in clinical populations using Automated Neuropsychological Assessment Metrics (ANAM) tests. Arch Clin Neuropsychol. Februar 2007;22:115–26.
86. George EO, Roys S, Sours C, Rosenberg J, Zhuo J, Shanmuganathan K, u. a. Longitudinal and prognostic evaluation of mild traumatic brain injury: A 1H-magnetic resonance spectroscopy study. J Neurotrauma. 1. Juni 2014;31(11):1018–28.
87. Sours C, Zhuo J, Roys S, Shanmuganathan K, Gullapalli RP. Disruptions in Resting State Functional Connectivity and Cerebral Blood Flow in Mild Traumatic Brain Injury Patients. PloS One. 2015;10(8):e0134019.
88. Banks SD, Coronado RA, Clemons LR, Abraham CM, Pruthi S, Conrad BN, u. a. Thalamic Functional Connectivity in Mild Traumatic Brain Injury: Longitudinal Associations With Patient-Reported Outcomes and Neuropsychological Tests. Arch Phys Med Rehabil. August 2016;97(8):1254–61.
89. Palacios EM, Yuh EL, Chang Y-S, Yue JK, Schnyer DM, Okonkwo DO, u. a. Resting-State Functional Connectivity Alterations Associated with Six-Month Outcomes in Mild Traumatic Brain Injury. J Neurotrauma. 15. April 2017;34(8):1546–57.
90. Weinstein E, Turner M, Kuzma BB, Feuer H. Second impact syndrome in football: new imaging and insights into a rare and devastating condition: Case report. J Neurosurg Pediatr. März 2013;11(3):331–4.
91. Compston A. Editorial. Brain. 1. November 2010;133(11):3157–9.
92. Signoretti S, Lazzarino G, Tavazzi B, Vagnozzi R. The Pathophysiology of Concussion. PM&R. Oktober 2011;3:S359–68.
93. Hughes RH, Silva VA, Ahmed I, Shreiber DI, Morrison B. Neuroprotection by genipin against reactive oxygen and reactive nitrogen species-mediated injury in organotypic hippocampal slice cultures. Brain Res. Januar 2014;1543:308–14.
94. Mahendru V, Sinha A, Bilotta F, Tewari A. Antioxidants: The new frontier for translational research in cerebroprotection. J Anaesthesiol Clin Pharmacol. 2014;30(2):160.
95. Clond MA, Lee B-S, Yu JJ, Singer MB, Amano T, Lamb AW, u. a. Reactive Oxygen Species-Activated Nanoprodrug of Ibuprofen for Targeting Traumatic Brain Injury in Mice. Borlongan CV, Herausgeber. PLoS ONE. 24. April 2013;8(4):e61819.
96. Stoica BA, Loane DJ, Zhao Z, Kabadi SV, Hanscom M, Byrnes KR, u. a. PARP-1 Inhibition Attenuates Neuronal Loss, Microglia Activation and Neurological Deficits after Traumatic Brain Injury. J Neurotrauma. 15. April 2014;31(8):758–72.
97. Globus MY-T, Alonso O, Dietrich WD, Busto R, Ginsberg MD. Glutamate Release and Free Radical Production Following Brain Injury: Effects of Posttraumatic Hypothermia. J Neurochem. 23. November 2002;65(4):1704–11.
98. Mcdonald JW, Althomsons SP, Hyrc KL, Choi DW, Goldberg MP. Oligodendrocytes from forebrain are highly vulnerable to AMPA/kainate receptor-mediated excitotoxicity. Nat Med. März 1998;4(3):291–7.
99. Grossman SD, Wolfe BB, Yasuda RP, Wrathall JR. Alterations in AMPA Receptor Subunit Expression after Experimental Spinal Cord Contusion Injury. J Neurosci. 15. Juli 1999;19(14):5711–20.
100. Hamm RJ, O'Dell DM, Pike BR, Lyeth BG. Cognitive impairment following traumatic brain injury: the effect of pre- and post-injury administration of scopolamine and MK-801. Cogn Brain Res. Dezember 1993;1(4):223–6.
101. Bullock R, Kuroda Y, Teasdale GM, Mcculloch J. Prevention of Post-Traumatic Excitotoxic Brain Damage with NMDA Antagonist Drugs: A New Strategy for the Nineties. In: Silva AM, Melo AR, Loew F, Herausgeber. Neurotraumatology: Progress and

Perspectives [Internet]. Vienna: Springer Vienna; 1992 [zitiert 29. November 2021]. S. 49–55. Verfügbar unter: http://link.springer.com/10.1007/978-3-7091-9233-7_15
102. Shapira Y, Yadid G, Cotev S, Niska A, Shohami E. Protective Effect of MK801 in Experimental Brain Injury. J Neurotrauma. Januar 1990;7(3):131–9.
103. Shohami E, Biegon A. Novel Approach to the Role of NMDA Receptors in Traumatic Brain Injury. CNS Neurol Disord - Drug Targets. 31. Juli 2014;13(4):567–73.
104. Singh N, Hopkins SJ, Hulme S, Galea JP, Hoadley M, Vail A, u. a. The effect of intravenous interleukin-1 receptor antagonist on inflammatory mediators in cerebrospinal fluid after subarachnoid haemorrhage: a phase II randomised controlled trial. J Neuroinflammation. Dezember 2014;11(1):1.
105. Tehranian R, Andell-Jonsson S, Beni SM, Yatsiv I, Shohami E, Bartfai T, u. a. Improved Recovery and Delayed Cytokine Induction after Closed Head Injury in Mice with Central Overexpression of the Secreted Isoform of the Interleukin-1 Receptor Antagonist. J Neurotrauma. August 2002;19(8):939–51.
106. Lucas S-M, Rothwell NJ, Gibson RM. The role of inflammation in CNS injury and disease: The role of inflammation in CNS. Br J Pharmacol. Januar 2006;147(S1):S232–40.
107. Jones NC, Prior MJW, Burden-Teh E, Marsden CA, Morris PG, Murphy S. Antagonism of the interleukin-1 receptor following traumatic brain injury in the mouse reduces the number of nitric oxide synthase-2-positive cells and improves anatomical and functional outcomes. Eur J Neurosci. Juli 2005;22(1):72–8.
108. Adamczak SE, de Rivero Vaccari JP, Dale G, Brand FJ, Nonner D, Bullock Mr, u. a. Pyroptotic Neuronal Cell Death Mediated by the AIM2 Inflammasome. J Cereb Blood Flow Metab. April 2014;34(4):621–9.
109. Clausen F, Hånell A, Israelsson C, Hedin J, Ebendal T, Mir AK, u. a. Neutralization of interleukin-1β reduces cerebral edema and tissue loss and improves late cognitive outcome following traumatic brain injury in mice: IL-1β inhibition improves outcome after TBI. Eur J Neurosci. Juli 2011;34(1):110–23.
110. Clausen F, Hånell A, Björk M, Hillered L, Mir AK, Gram H, u. a. Neutralization of interleukin-1β modifies the inflammatory response and improves histological and cognitive outcome following traumatic brain injury in mice. Eur J Neurosci. August 2009;30(3):385–96.
111. Xiao G, Wei J, Yan W, Wang W, Lu Z. Improved outcomes from the administration of progesterone for patients with acute severe traumatic brain injury: a randomized controlled trial. Crit Care. 2008;12(2):R61.
112. Chatzipanteli K, Alonso OF, Kraydieh S, Dietrich WD. Importance of Posttraumatic Hypothermia and Hyperthermia on the Inflammatory Response after Fluid Percussion Brain Injury: Biochemical and Immunocytochemical Studies. J Cereb Blood Flow Metab. März 2000;20(3):531–42.
113. Chatzipanteli K, Yanagawa Y, Marcillo AE, Kraydieh S, Yezierski RP, Dietrich WD. Posttraumatic Hypothermia Reduces Polymorphonuclear Leukocyte Accumulation Following Spinal Cord Injury in Rats. J Neurotrauma. April 2000;17(4):321–32.
114. Kinoshita K, Chatzipanteli K, Vitarbo E, Truettner JS, Alonso OF, Dietrich WD. Interleukin-1β Messenger Ribonucleic Acid and Protein Levels after Fluid-Percussion Brain Injury in Rats: Importance of Injury Severity and Brain Temperature. Neurosurgery. 1. Juli 2002;51(1):195–203.
115. Vitarbo EA, Chatzipanteli K, Kinoshita K, Truettner JS, Alonso OF, Dietrich WD. Tumor Necrosis Factor α Expression and Protein Levels after Fluid Percussion Injury in Rats: The Effect of Injury Severity and Brain Temperature. Neurosurgery. 1. August 2004;55(2):416–25.
116. Tomura S, de Rivero Vaccari JP, Keane RW, Bramlett HM, Dietrich WD. Effects of Therapeutic Hypothermia on Inflammasome Signaling after Traumatic Brain Injury. J Cereb

Blood Flow Metab. Oktober 2012;32(10):1939–47.
117. Dietrich WD. The importance of brain temperature in cerebral injury. J Neurotrauma. Mai 1992;9 Suppl 2:S475-485.
118. Tsai S-J. Preventive potential of low intensity pulsed ultrasound for chronic traumatic encephalopathy after repetitive head collisions in contact sports. Med Hypotheses. Januar 2020;134:109422.
119. Shi X, Tang Z, Sun D, He X. Evaluation of hyperbaric oxygen treatment of neuropsychiatric disorders following traumatic brain injury. Chin Med J (Engl). 5. Dezember 2006;119(23):1978–82.
120. Tal S, Hadanny A, Berkovitz N, Sasson E, Ben-Jacob E, Efrati S. Hyperbaric oxygen may induce angiogenesis in patients suffering from prolonged post-concussion syndrome due to traumatic brain injury. Restor Neurol Neurosci. 4. November 2015;33(6):943–51.
121. Rockswold SB, Rockswold GL, Zaun DA, Zhang X, Cerra CE, Bergman TA, u. a. A prospective, randomized clinical trial to compare the effect of hyperbaric to normobaric hyperoxia on cerebral metabolism, intracranial pressure, and oxygen toxicity in severe traumatic brain injury: Clinical article. J Neurosurg. Mai 2010;112(5):1080–94.
122. Palzur E, Zaaroor M, Vlodavsky E, Milman F, Soustiel JF. Neuroprotective effect of hyperbaric oxygen therapy in brain injury is mediated by preservation of mitochondrial membrane properties. Brain Res. Juli 2008;1221:126–33.
123. Boussi-Gross R, Golan H, Fishlev G, Bechor Y, Volkov O, Bergan J, u. a. Hyperbaric Oxygen Therapy Can Improve Post Concussion Syndrome Years after Mild Traumatic Brain Injury - Randomized Prospective Trial. Ai J, Herausgeber. PLoS ONE. 15. November 2013;8(11):e79995.
124. Duan S, Shao G, Yu L, Ren C. Angiogenesis contributes to the neuroprotection induced by hyperbaric oxygen preconditioning against focal cerebral ischemia in rats. Int J Neurosci. 3. August 2015;125(8):625–34.
125. Janak JC, Cooper DB, Bowles AO, Alamgir AH, Cooper SP, Gabriel KP, u. a. Completion of Multidisciplinary Treatment for Persistent Postconcussive Symptoms Is Associated With Reduced Symptom Burden. J Head Trauma Rehabil. Februar 2017;32(1):1–15.
126. Minen M, Jinich S, Vallespir Ellett G. Behavioral Therapies and Mind-Body Interventions for Posttraumatic Headache and Post-Concussive Symptoms: A Systematic Review: Headache. Headache J Head Face Pain. Februar 2019;59(2):151–63.
127. Han K, Chapman SB, Krawczyk DC. Cognitive Training Reorganizes Network Modularity in Traumatic Brain Injury. Neurorehabil Neural Repair. Januar 2020;34(1):26–38.
128. Broglio SP, Cantu RC, Gioia GA, Guskiewicz KM, Kutcher J, Palm M, u. a. National Athletic Trainers' Association Position Statement: Management of Sport Concussion. J Athl Train. 1. März 2014;49(2):245–65.
129. Leddy JJ, Sandhu H, Sodhi V, Baker JG, Willer B. Rehabilitation of Concussion and Post-concussion Syndrome. Sports Health Multidiscip Approach. März 2012;4(2):147–54.
130. McCrory P, Meeuwisse W, Johnston K, Dvorak J, Aubry M, Molloy M, u. a. Consensus Statement on Concussion in Sport 3rd International Conference on Concussion in Sport Held in Zurich, November 2008. Clin J Sport Med. Mai 2009;19(3):185–200.
131. Cantu RV, Cantu RC. Athletic Head Injuries. In: Clinical Sports Medicine [Internet]. Elsevier; 2007 [zitiert 25. Februar 2022]. S. 323–30. Verfügbar unter: https://linkinghub.elsevier.com/retrieve/pii/B9781416024439500271
132. Sangobowale MA, Grin'kina NM, Whitney K, Nikulina E, St. Laurent-Ariot K, Ho JS, u. a. Minocycline plus N-Acetylcysteine Reduce Behavioral Deficits and Improve Histology with a Clinically Useful Time Window. J Neurotrauma. April 2018;35(7):907–17.
133. Haber M, James J, Kim J, Sangobowale M, Irizarry R, Ho J, u. a. Minocycline plus N-acteylcysteine induces remyelination, synergistically protects oligodendrocytes and modifies

neuroinflammation in a rat model of mild traumatic brain injury. J Cereb Blood Flow Metab. August 2018;38(8):1312–26.
134. Breen PW, Krishnan V. Recent Preclinical Insights Into the Treatment of Chronic Traumatic Encephalopathy. Front Neurosci. 7. Juli 2020;14:616.
135. Hynynen K, McDannold N, Vykhodtseva N, Jolesz FA. Noninvasive MR Imaging–guided Focal Opening of the Blood-Brain Barrier in Rabbits. Radiology. September 2001;220(3):640–6.
136. Jordão JF, Ayala-Grosso CA, Markham K, Huang Y, Chopra R, McLaurin J, u. a. Antibodies targeted to the brain with image-guided focused ultrasound reduces amyloid-beta plaque load in the TgCRND8 mouse model of Alzheimer's disease. PloS One. 11. Mai 2010;5(5):e10549.
137. Samiotaki G, Acosta C, Wang S, Konofagou EE. Enhanced delivery and bioactivity of the neurturin neurotrophic factor through focused ultrasound-mediated blood--brain barrier opening in vivo. J Cereb Blood Flow Metab Off J Int Soc Cereb Blood Flow Metab. 31. März 2015;35(4):611–22.
138. Chen C-M, Wu C-T, Yang T-H, Liu S-H, Yang F-Y. Preventive Effect of Low Intensity Pulsed Ultrasound against Experimental Cerebral Ischemia/Reperfusion Injury via Apoptosis Reduction and Brain-derived Neurotrophic Factor Induction. Sci Rep. 3. April 2018;8(1):5568.
139. Li H, Sun J, Zhang D, Omire-Mayor D, Lewin PA, Tong S. Low-intensity (400 mW/cm2, 500 kHz) pulsed transcranial ultrasound preconditioning may mitigate focal cerebral ischemia in rats. Brain Stimulat. Juni 2017;10(3):695–702.

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