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Neuroprotective Measures in Traumatic Brain Injury Patients

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SUMMARY

Traumatic brain injury has been described as the "most complicated disease of the most complicated organ". That statement appears to hold weight, with both its epidemiologic analysis and medical treatment of the disease being topics of active and evolving debate. Current treatment is primarily driven by avoiding life-threatening complications and maintaining perceived optimal body homeostasis. This is immensely important and the basis of further treatment. However, given our continuously evolving understanding of the pathophysiologic processes behind the disease, it appears inevitable to have our treatment approaches evolve alongside our understanding. Studies at varying levels of advancement are exploring the idea of neuroprotective measures in traumatic brain injury patients – pushing the envelope of what level of care clinicians may be able to provide this historically underserved, heterogeneous patient population.

KEYWORDS

TBI, Traumatic Brain Injury, Neuroprotection, Secondary Injury Prevention, Brain Trauma

LIST OF ABBREVIATIONS

ABBREVIATION	MEANING
TBI	Traumatic brain injury

Fig.	Figure
GCS	Glasgow Coma Scale
ICP	Intracranial pressure
CBF	Cerebral blood flow
CTE	Chronic traumatic encephalopathy
DAI	Diffuse axonal injury
MRI	Magnetic resonance imaging
MVA	Motor vehicle accident
DAMP	Damage-associated molecular pattern
BBB	Blood-brain-barrier
RCT	Randomized clinical trial
CT	Computed tomography
EEG	Electroencephalography
BTF	Brain trauma foundation
MAP	Mean arterial pressure
ROS	Reactive oxygen species
PTS	Post-traumatic seizures
NAC	N-acetyl L-cysteine
HBO	Hyperbaric oxygen therapy

INTRODUCTION

Traumatic brain injury (TBI) is a commonly encountered phenomenon in the intensive care unit and one of the leading causes of death and disability in trauma patients worldwide. Within Europe is a wide distribution of Incidence present, but even at the low end (200-299 cases per 100.000) it is a problem at scale (Fig. 1). On the global scale, it is estimated to affect 69,000,000 individuals worldwide each year, with Europe having an overall incidence per 100,000 people of 1012 patients (1). However, this data may be a conservative estimate, as TBI is also known as the “Silent Epidemic” due to a deficiency in epidemiological data for the civilian sector. Increased usage of motor vehicles has led to an increase in TBI prevalence, especially in high-income and developing countries. Exact data is debated, but the generally high incidence is indisputable, and the high importance for a clinician to be familiar with the matter, no matter their geographic location, is given. A noteworthy subspecialty dealing with and providing much data on the topic is military medicine, as TBI is one of the leading causes of death and long-term disability associated with military conflicts, represented in 8% of combat wounds during Operation Iraqi Freedom and Operation Enduring Freedom being of the head (2).

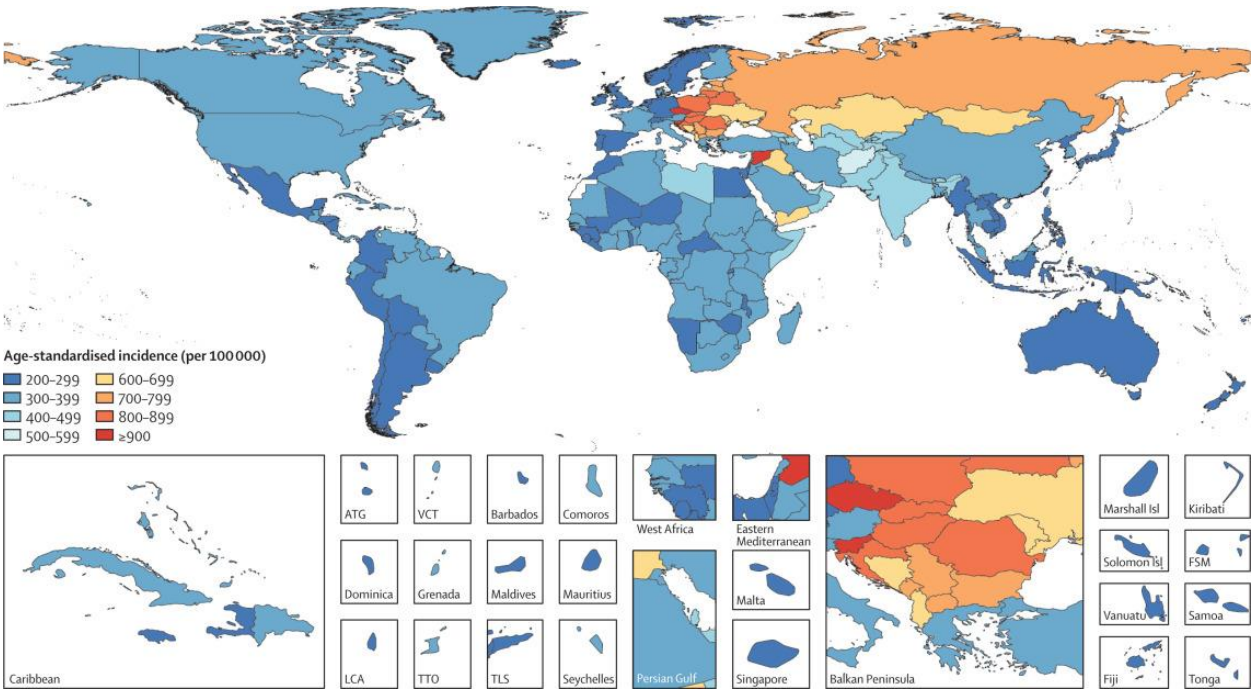

Fig. 1: Map showing recorded age-standardized incidence of TBI per 100,000 per country (3)

Underreporting of TBI-affected patients is likely substantial, especially in those with mild brain injuries, both due to patients not seeking medical treatment, more severe health conditions masking accompanying TBI, but also symptoms and neuropsychological changes not being attributed to a prior traumatic injury. There is also significant ongoing research into a type of multi-hit model of TBI, as is for example commonplace in contact sports, sometimes referred to as chronic traumatic encephalopathy (4). Some changes between ICD-9 and ICD-10 (which are in the first place administrative tools before clinical classifications) further limit the ability to utilize existing data in a compatible fashion. Another roadblock to the adequate epidemiological examination of TBI is a general lack of good quality monitoring at a state and international level. A good source of information within the European Union is the Collaborative European NeuroTrauma Effectiveness Research in TBI (CENTER-TBI). There are efforts to streamline and improve study quality, data collection, and study models to understand the disease and its potential therapies (5). One such model is the currently being built ENIGMA (Enhancing Neuroimaging Genetics through Meta-Analysis) working group, which aims to utilize large-scale neuroimaging data analysis to enable investigators to better test hypotheses about recovery and morbidity in moderate and severe adult TBI (6). Big data international framework approaches like these hold promise in a field dominated by small study sizes.

TBI specifically refers to a direct structural injury to, as well as secondary disruptions of normal function of, the brain as a result of blunt or penetrating head trauma. TBI has a primary component – the immediate injury as sustained at the time of the trauma, and a secondary component – the indirect injury resulting from both physiological changes triggered by the insult and acute measures to manage TBI. Long-term disability as a consequence of TBI in the patient population often presents as neurological symptoms and deficits linked to both the primary and the secondary brain injury sustained. Notable is that while the primary brain injury is hard to ameliorate (except through preventative measures such as helmets and seatbelts), the extent of secondary brain injury is heavily dependent on clinical management and thus the topic of major debate as prognoses for TBI depend on it. Despite this is the current data situation advising management of these patients based on fairly weak evidence, with much clinical practice relying on accumulated clinical experience, changing as new data emerges and multiple novel potential approaches to management existing.

This paper aims to present some information on managing TBI in a neuroprotective way, mostly in the context of critical care, with the overarching goal to minimize secondary injury. This thesis paper aims to establish an understanding of TBI and its surrounding approaches, enumerate some new data that has come out since the last edition of the Brain Trauma Foundation (BTF) guidelines (2016) and elaborate on them. Lastly, some potentially actionable data that emerged since the last BTF guidelines is considered.

LITERATURE SEARCH STRATEGY

A starting point in literature to gain an understanding of treatment as it is typically done at the time of literature search were the guidelines published by the Brain Trauma Foundation. (7) Specifically: Guidelines for the Management of Severe TBI, 4th Ed (8).; Guidelines for Prehospital Management of TBI,2nd Ed.; Early Indicators of Prognosis in Severe TBI; Guidelines for the Surgical Management of TBI (last update 2006). These lay the groundwork for understanding the treatment of TBI with a special focus on neuroprotection, upon which this literature review will build its elaboration and examination of more recent data points. Assisting in this is an UpToDate review, as well as a ClinicalKey review. Another source of information is the website: https://www.center-tbi.eu.

For the most up-to-date understanding and evaluation of the current research landscape regarding TBI management, with a focus on neuroprotection, some searches on pubmed.ncbi.nlm.nih.gov were performed with the following search terms: “traumatic brain injury”, “traumatic brain injury neuroprotection” “TBI”. The initial search was unrestricted, but closer attention was paid to papers published between 2016 and 2022, as 2016 was the time of publication of the 4th Edition Guidelines for the Management of Severe TBI by the Brain Trauma Foundation. Special attention was paid to clinical trials, meta-analyses, systematic reviews, and randomized controlled trials (RCTs) within this period. “traumatic brain injury neuroprotection” between 2016-2021 for these criteria yielded 79 results at the time of research.

BRIEF OVERVIEW OF TRAUMATIC BRAIN INJURY, ITS MECHANISMS, PATHOLOGY, MANAGEMENT, AND POTENTIAL OPPORTUNITIES FOR APPROACHES

The definition of TBI varies as one would expect from something referred to as “the most complex disease in the most complex organ”, but for the purposes of this paper, it is interpreted as an impact to the head, which results in varying levels of immediate and delayed, chemical, cellular, and macroscopic changes, detected with clinical examinations and imaging studies. It is typically subdivided into mild, moderate, and severe TBI. TBI as a term in clinical usage is exceptionally broad and breaks down notional barriers between neurology and psychiatry. In its early course, it also frequently requires multimodal treatment at the full attention of medical specialists of traumatology, neurosurgery, intensive care, anesthesiology, nursing, as well as neurology, and psychiatry – sometimes more due to the inherent multimorbidity of the disease etiology, but also due to the inherent spectrum of the disease. In milder forms, it may also describe neuropsychological changes occurring some time after an injury involving the head.

Mild TBI is typically defined as a loss of consciousness of fewer than 30 minutes, as well as a Glasgow Coma Scale (GCS) of 13-15 and unremarkable imaging.

Moderate TBI is typically defined as a loss of consciousness of 30 minutes to 24 hours with even longer alteration in consciousness, a GCS of 9-12, and can present with abnormal imaging.

Severe TBI is defined as more than 24 hours of loss of consciousness, a GCS of 3-8, and prolonged posttraumatic amnesia, and can present with abnormal imaging.

Additional to severity, TBI can be classified according to the anatomical features of the injury. This typically refers to lesions as they are seen on imaging, with lesions being extra-axial or intra-axial, focal or diffuse. In most severe cases of TBI, these lesions are seen concomitantly. Of special note is diffuse axonal injury, which manifests with minimal or absent damage visible on imaging studies, but strong clinical or post-mortem indicators of TBI. This is an important aspect of TBI, as perceived severity in imaging may not be correlated clinically.

There are calls to reiterate the phenotyping of TBI to include more data points to improve their descriptive quality, such as single nucleotide polymorphisms in sites associated with TBI prognosis, ongoing ICP (Intracranial Pressure) trajectory, or CBF autoregulation impairment, as the beforementioned classification is primarily based on initial clinical status (5).

TBI has a multitude of etiologies, all leading to the common injury pathway of head trauma. These are primarily falls, motor vehicle accidents, and assaults. Sports and recreation-related TBIs are more common in children, although pediatric TBI has separate guidelines and considerations.

Mild TBI will be comparatively neglected in this paper since most neuroprotection in this subclassification consists of interventions aimed to prevent the development of specific persistent symptoms or those aimed to ameliorate symptoms or disorders becoming evident in the course of MTBI. This neglect is not ideal, as mild TBI and its entities, such as chronic traumatic encephalopathy (CTE), are tremendously impactful and underreported, while still not ideally understood, at least partially due to their inherent heterogeneity (9,10).

The typical TBI patient would present with associated signs of head trauma. These include, but are not limited to, bruises, scalp lacerations, unequal pupil dilation, airbag burns, road rash on the head, as well as very indicative signs such as periorbital hematoma or mastoid hematoma – skull fracture suggestions – which are commonly associated with TBI. Symptoms may include headache, nausea, vomiting, seizures, altered mental status, and can progress to coma and even death.

Imagery is heterogeneous, with some comatose patients having no discernible pathologies on imaging. Common lesions that are seen however are bleeds and focal collections of blood in or around the brain – both intra-axially as intracerebral hemorrhages, as well as extra-axially in epidural and subdural hematomas, as well as subarachnoid and intraventricular hemorrhages. Of

note is that lesions commonly appear after initial imaging, and therefore a second round of neuroimaging within 24 hours is indicated in all comatose patients, or more rapidly in those with substantial clinical worsening and ICP rises (11). A bit rarer form of focal injury are cerebral lacerations, which describe tissue being cut or torn apart. A harder to detect injury is diffuse axonal injury (DAI), in which white matter tracts are subjected to shearing force. These may be seen as multiple small lesions within the white matter tract but may also be invisible, even on the more sensitive MRI neuroimaging.

If an injury is manifest focally, it will commonly produce symptoms related to regular functions of the damaged area. An example would be the common injuries in MVAs – lesions to the orbitofrontal cortex and anterior temporal lobes – leading to later deficits in behavior, emotion, and olfaction.

An invaluable tool in the initial assessment of trauma patients for TBI is the previously mentioned Glasgow Coma Scale (GCS) (12), which objectively describes the extent of impaired consciousness on a numeric scale from 3-15 and can be used in patients older than 5 years of age to classify the severity of TBI. It is divided into three parameters that are graded according to their best response: eye response, verbal response, motor response, with maximum values of respectively 4 (best eye-opening response), 5 (best verbal response), and 6 (best motor response) – totaling a maximum 15, minimum 3. These scores are then cumulatively interpreted according to the previous severity grading (but can also be interpreted according to individual elements, e.g. E2V3M4).

The GCS has noteworthy caveats that may interfere with an accurate assessment and thus will need to be excluded if this diagnostic tool is to be used. These factors generally impair areas of measurement but are not of a neurologic origin. They include but are not limited to: language barriers, preexisting intellectual or neurological deficit, hearing loss or speech impediment, as well as the sedating or paralyzing effects of current pharmacological and physical treatment. Some injuries, such as cranial fractures or spinal cord lesions, may also have an undue impact and give a falsely low score, causing confusion. In patients at the lower end of the GCS scale, such as intubated patients, the Full Outline of Unresponsiveness (FOUR) score can also be utilized to perform an assessment (13).

TBI is a complex and heterogeneous problem, often better understood as a syndrome than a singular disease. As previously mentioned, it is divided into a primary and a secondary injury, with the primary injury happening as a direct consequence of the impact on the brain at the time of injury, while the secondary injury occurs minutes or days after, as a consequence of a multitude of processes – potentiated through the prior primary injury.

Primary Brain Injury

Primary injury occurs at the time of trauma. It may occur in two ways: closed brain injury or penetrating brain injury. Very rapid acceleration and deceleration too are a fairly common injury mechanism. Blast waves on their own too can cause TBI; this is primarily seen in military medicine as a result of an IED (Improvised explosive device) attack. In general, the result of these very diverse mechanisms of injury is force being transferred to intracranial tissue and blood vessels. Resultant damage includes focal injury as well as diffuse injury. Hematomas from injured blood vessels, but also classical shearing of white matter tracts and focal, as well as global cerebral edema. Hematomas/hemorrhages commonly encountered include epidural and subdural hematomas, as well as subarachnoid and intraventricular hemorrhages on the extra-axial side, as well as intraparenchymal hemorrhages on the intraaxial side. The shearing injury of white matter tracts is named diffuse axonal injury (DAI) and is often hard to evaluate on imaging, manifesting its clinically pronounced form through profound coma and poor outcomes, despite normal intracranial pressure (ICP). This shearing and stretching can also lead to a disruption of the myelin sheath, causing dysregulation of transmembrane ion fluxes, which ultimately leads to impaired axonal transport and further contributes to the brain's vulnerability to secondary injury - specifically local secondary axotomy and demyelination (11) plus their downstream consequences. Cerebral edema can also occur even early on in TBI and is sometimes attributed to primary brain injury.

Secondary Brain Injury

A series of macroscopic, molecular, cellular, inflammatory events and cascades, which can cause damage both directly and indirectly, and over hours, days, even weeks, years after the primary brain injury. These events may, on their own, be of lesser significance, but in the context of the prior primary brain injury, they have a greatly exacerbated impact on the previously made vulnerable brain. The same applies to unrelated conditions, e.g., hypotension/hypoxia, which the

brain would normally be able to handle without significant damage, but in the context of TBI, cause tangible injury and are a major prognostic factor (14). Further potentiated is this by cerebral autoregulation and its potential for becoming untethered from tissue requirements. These events do occur intracranially, and the majority of this paper will concern itself with those, but TBI at this point may be better understood as a systemic disease as well as a local one, presenting with, e.g., coagulopathies and electrolyte imbalances. Other mechanisms of injury are mitochondrial dysfunction, neurotransmitter-mediated toxicity, free-radical injury, inflammatory responses and over-responses, apoptosis, vasospasms, microvascular occlusion, vascular injuries (large and small vessel) – all pathways TBI shares with ischemic injuries following stroke. These directly lead to neuronal cell death but also cause macroscopic swelling of the brain, increasing ICP. Some of these injurious pathways can be grouped together by their downstream effects despite differences in intermediate steps – Figures 2 and 3 schematically represent this.

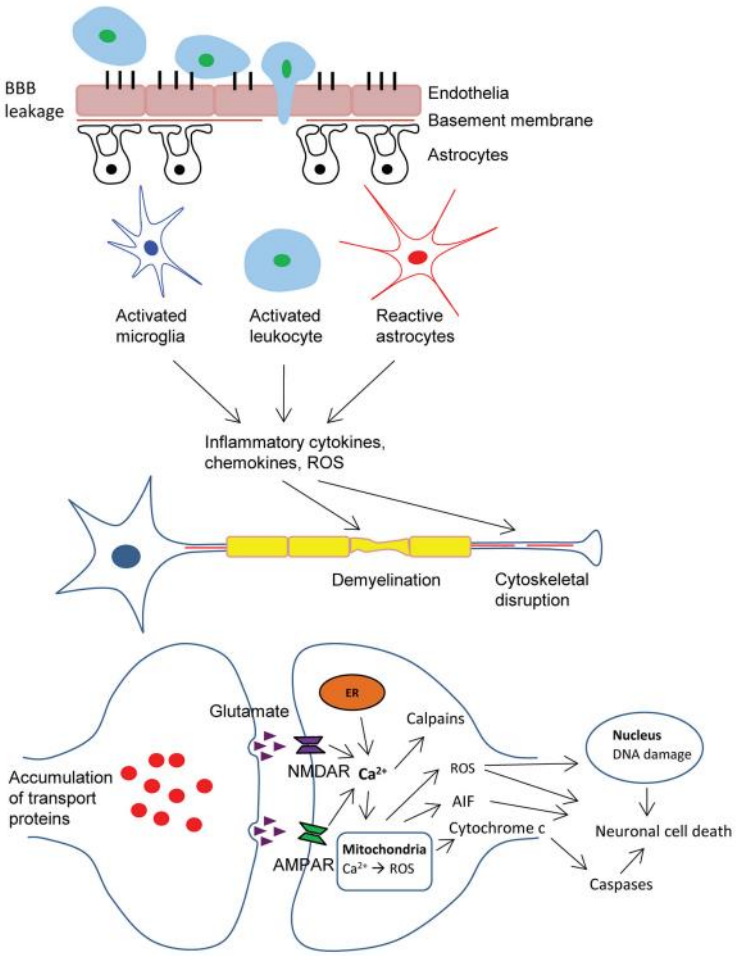

Fig. 2: Schematic representation of part of traumatic brain injury pathology. (15)

A notable molecular pathway of injury is the damage-associated molecular pattern (DAMP). DAMPs are released from injured cells into the extracellular matrix, stimulating local immune cells to release inflammatory mediators, including chemotactics, attracting granulocytes to the injury site, where they begin to phagocytose the debris. This is simultaneous to a blood-brain-barrier (BBB) impairment, which allows the entry of circulating inflammatory cells into the cerebral parenchyma. A little later, monocytes and glia activate increasingly to perform further phagocytosis and begin the first repair of parenchyma. As part of this process, activated microglia also release various neurotoxic substances, mainly reactive oxygen species and excitatory neurotransmitters. Both of these are implicated in furthering secondary injury and subjects of study, presenting as a "double-edged sword of neuroprotection", both exacerbating tissue damage through inflammatory and scarring mechanisms but also ameliorating existing damage through tissue repair and neurogenesis. It is also at this point in time when T and B lymphocytes can begin to appear (days 3-7 post primary trauma) (16). Of note is that these T and B cells may persist at the site of injury for months and present another potential vector for neuroprotective measures. Modifying this inflammation has been the subject of many studies, one of the most well-known being the MRC CRASH trial, showing a contraindication for high-dose steroids in severe TBI (17). However, a study into the effect of perispinal etanercept, a TNF (tumor necrosis factor) inhibitor, has shown tentative improvement, reducing motor impairment and spasticity in TBI patients even more than 10 years after the initial injury (18). Various other Interleukin inhibitors have shown promising results in animal models (19–22) and have the potential for future research into the role of immunomodulation in the treatment of TBI. There is some crossover between prospective agent effects, as, e.g., cannabidiol has been shown to ameliorate the neurological deficit score after TBI in rats, suspectedly through both reducing the level of proinflammatory cytokines but also increasing the expression of tight junction proteins, as well as ameliorating blood-brain barrier disruption, making it an example of a potential future multi-pronged neuroprotective agent (23).

Another cascade of interest is the excitotoxicity of freely released neurotransmitters, with the prime example being glutamate, leading to over-activation of their receptors, which has been shown to cause Blood-Brain-Barrier damage and general loss of neuronal membrane integrity. Free glutamate's delirious effect is potentiated by a failure of glutamate re-uptake through a decline in glutamate transporters post-TBI (15). This combination ultimately leads to further cellular loss

and cerebral edema – of interest since a mouse study has shown the administration of membrane-resealing polymers improves functional recovery (24). Additionally, persistently elevated cerebral tissue glutamate has been linked with TBI severity (25), and glutamate is one of the substances modern cerebral microdialysis can measure.

Oxidative stress is another highly relevant secondary injury pathway of TBI. The already quite high levels of physiologic oxidant and antioxidant production are disrupted and the parenchyma is overwhelmed by reactive oxygen species (26). This is amplified by the brain's abundance of iron present, as this iron, once released from its carrying proteins, will actively catalyze Fenton's reaction and generate reactive oxygen species. This sequence has been the rationale for iron chelation as part of TBI treatment – thus far, with no human success but promising animal model results (27–29), the latest of which has been published in 2019. Animal studies have also shown benefits to the application of superoxide radical scavenger after TBI (30), but this too has yet to be significantly replicated in human studies. An early study examining the prospect of using cyclosporin as a neuroprotectant suspected of ameliorating this mechanism of injury has had first results of safety in a low N of human patients with careful renal monitoring, demonstrated the pharmaceuticals ability to pass the injured BBB, as well as a tentative positive effect on TBI injury biomarkers (31). This makes it a contender for a true neuroprotectant in the future. A fairly advanced field of research in this pathway concerns N-acetylcysteine and N-acetylcysteine amide administration post-TBI, reporting significantly improved neurofunctional outcomes and downregulation of inflammatory and oxidative stress markers at the tissue level, although controlled clinical investigations are still required before recommendations can be established (32).

Some other notable compounds currently under investigation for their tentative success as a neuroprotectant in the context of TBI, but without clear recommendations for usage, are Statins (33), Metformin, docosahexaenoic acid, vitamin D, Cerebrolysin (34), and Memantine (35).

A small size RCT of 30 TBI patients with half receiving 1g Metformin every 12 hrs for five days, and the other half being the control group – receiving usual management. As markers of efficacy, temporal profiles of TBI biomarkers were utilized – specifically serum S100b, neutrophil to lymphocyte ratio, and glial fibrillary acidic protein. Biomarkers showed statistically significant declines in S100b and NLR levels, with no hypoglycemia and lactic acidosis occurring, making

metformin a potentially safe, effective therapeutic option in these patients. However, the study's significance depends upon the prognostic value of the analyzed biomarkers, which are widely accepted to be given (36).

Docosahexaenoic acid has been postulated to be an effective neuroprotectant in TBI – with rat model studies showing a protective effect against TBI-induced motor deficits (37), postulated to have their effect through the Nrf2-ARE signaling pathway. This particular component is interesting because of its potential as a prophylactic neuroprotectant. A potential benefit for athletes competing in sports with high incidence rates of CTE (e.g., 61% of NFL players experience at least 1 concussion within their careers) (4). A dosage exploration study on American football athletes showed the treatment group experiencing attenuation of Serum Neurofilament Light (a biomarker of axonal injury) compared to the placebo group, indicating a potential practice for prophylactic neuroprotectants (38). Another potential neuroprotectant in need of further study is oral vitamin D, with a study indicating level of consciousness improvements in the n=20 treatment group vs. the n=15 placebo group (39).

Programmed cell death (PCD) on its own is a physiologic process, but after TBI, a dramatic increase in its expression is observed, leading to poor prognosis associated neuronal cell loss. This follows in the multiple known pathways of apoptosis, giving interest to the possibility of interfering, a current subject of studies, none of which have come to the human model yet (15).

Brain Herniation

This is a displacement of brain tissue through an anatomic opening into another part of the cranium and is typically a response to increased ICP. This can happen both early and late. Some common reasons for brain herniation include hematomas and hemorrhages, but diffuse brain swelling is also a reason for occurrence. Brain herniation can lead to compression of vital structures, resulting in a multitude of disagreeable effects up to death. It is mentioned here as one of the primary focuses in the clinical management of TBI is the prevention of this occurring, and therapies used to mitigate an elevated ICP include hyperosmolar agents, barbiturates, hypothermia, and craniectomy.

TBI patients often require a high level of monitoring to prevent their fragile homeostasis from reaching levels injurious to the already insulted brain. Monitoring of ICP and cerebral perfusion pressure (CPP) are the cornerstone of brain-focused monitoring of these patients (11). In recent

years neurocritical care has become much more advanced, including the usage of brain multi-modality monitoring, with patients commonly receiving intracranial "Triple Bolt" systems, consisting of an ICP monitor, a brain tissue oxygenation monitor, as well as a cerebral microdialysis catheter. The ICP monitor is used to establish intracranial pressure, as well as to calculate cerebral perfusion pressure and pressure reactivity index – all surrogate markers of brain tissue metabolic supply. Pressure- reactivity -index can serve to establish the level of optimum autoregulation, maintaining the level which has been shown to be associated with better outcomes (11). The brain tissue oxygenation monitor serves to analyze local brain tissue oxygenation. The cerebral microdialysis catheter allows for analyzing local levels of lactate and pyruvate, which in turn can be used to calculate their ratio – giving insight into the local metabolic state of brain parenchymal tissue. These units can also analyze local levels of glucose(energy substrate), glycerol (a marker of loss of cellular structural integrity (11)), and glutamate (an early marker of cerebral ischemia (11)). In a more research-focused role can the molecular cutoff membrane of the intracerebral microdialysis catheter be adjusted in order to harvest interstitial proteins of interest (40). The clinical value of this intense and invasive multimodal monitoring is supported by low-level evidence, with trials both ongoing and required.

ICP management is one of the cornerstones of TBI management, recognition of ICP crisis is vital. In patients with questionable ICP, the bar to inserting a direct probe is fairly low, and the level of diagnostic suspicion, even preclinically and in the emergency setting, is fairly high. If a patient presents with neurologic decay, anisocoria, or posturing – empiric osmotic treatment is reasonable while awaiting more definitive diagnostic measures – typically a head CT scan. Although elevated ICP is generally approached as a disease, is it worthwhile to remember it being a symptom of multiple, often coexisting, processes. This doesn't much factor into current management strategies, save for hematoma evacuation/craniectomy, and possibilities targeting the underlying options are a focus of ongoing research (11). Management of elevated ICP takes a tiered approach, with options including elevation of the head of the bed, venous drainage (neck positioning, neck brace loosening) adjustment, optimizing sedation and analgesia, brief hyperventilation to decrease paCO2 and induce cerebral vasoconstriction, and osmotic agents forming the spearhead of a fast response (41). Osmotic agents available are generally mannitol and hypertonic saline, with the latter generally being preferred. Bolus of hypertonic saline has shown better effectiveness in lowering ICP after severe TBI than mannitol, although 2-week mortality was not different between

the two treatment groups (42). In patients with no surgically correctable causes of ICP elevation and treatment-refractory ICP > 20 mmHg barbiturate coma is an option; the prophylactic use of barbiturate therapy, however is not recommended (8,41). At a variable place in the treatment algorithm of elevated ICP is decompressive craniectomy, a procedure associated with fewer hours of elevated ICP but at significant risk of adverse events and with fairly poor prognosis, as one would expect from the clinical situation requiring this therapy (43).

Continuous electroencephalography (EEG) is routinely used in patients with post-traumatic seizures (PTS) or clinical suspicion thereof in paralyzed patients. The rate of early PTS may be as high as 12% for clinical PTS and 25% for subclinical seizures detected on EEG (8). Suppression of these seizures pharmacologically (traditionally using phenytoin) has data showing benefit both acutely and long-term.

Airway management is one of the core tenets in medicine as a whole, and this holds true in the treatment of TBI. TBI patients are at elevated risk of compromised respiratory drive and function, as well as pulmonary aspiration. Ventilation strategies can also be utilized in the treatment of cerebral herniation through transient prophylactic hyperventilation, but in most TBI patients normal physiologic ventilation is the currently advised goal (8). It is important to consider how directly linked PaCO2 levels in arterial blood, and cerebral blood blow (CBF) are, with a linear relation between 20-80 mm Hg PaCO2, with low PaCO2 leading to low CBF, possibly precipitating cerebral ischemia in a vulnerable brain – and high PaCO2 possibly leading to cerebral hyperemia and elevated ICP. Notable is that utilizing hyperventilation is to be avoided during the first 24h after injury, as CBF is often significantly reduced already. Its efficacy is also variable as it depends on an at least partially intact cerebral vascular autoregulation. If this technique is applied, it is recommended to monitor jugular venous oxygen saturation and/or brain tissue O2 partial (8).

Temperature management has been a topic of great debate in the context of TBI. The rationale being that hypothermia is recognized to preserve cells and tissue given metabolic challenge, with evidence on hypothermia after cardiac arrest from acute coronary syndromes showing benefit regarding neurologic outcomes (44). We should consider treatments' propensity to decrease ICP and the already existing infrastructure to administer this treatment. There are, however also risks associated with hypothermia, including coagulopathy and anti-inflammation – both of which have

an ambivalent effect on presumed TBI pathology. On its own, hypothermia can also commonly induce shivering, which in turn increases metabolic demand – worsening brain tissue oxygenation (45). Current BTF guidelines do not recommend the utilization of prophylactic hypothermia. However, fever management is something to be pursued, as fever increases metabolic demand, blood flow, and blood volume of an injured brain – worsening ICP control and potentiating various other mechanisms of secondary injury (46). Thus maintenance of normothermia is to be attempted with ferocity, even utilizing intravascular cooling catheters. One study on the usage of such cooling catheters showed benefits in the reduction of fever burden and intracranial hypertension burden(the latter both quantitatively and qualitatively) (46). Some guidelines prefer the utilization of surface cooling adhesive pads with continuous feedback-loop regulation to maintain normothermia for their ease of use, system price point, and non-invasive nature.

Glycemic control is typically done with a different acceptable window than might be expected, as a study comparing intensive insulin therapy to achieve a systemic glucose target between 80-120 mg/dL vs. a more intermediate 121-180 mg/dL found the former to be associated with reduced cerebral extracellular glucose availability, increased prevalence of brain energy crisis and in turn increased mortality (47). Hyperglycemia is associated with worsened outcomes in TBI (48), which could be due to increased tissue acidosis, ROS generator, and increased BBB permeability.

TBI patients have a multitude of possible reasons for requiring anesthetic and analgesic management in an emergency setting, in the context of ongoing intensive care management (e.g., ICP managing through pentobarbital coma (49)), for diagnostic imaging, for medical interventions (e.g., hematoma evacuation, craniotomy or decompressive craniectomy), but also to facilitate surgical treatment for extracranial injuries. Anesthesia may induce secondary injuries to the vulnerable brain through ICP variations, hypotension, hypoxemia, hypercarbia, hypocarbia (with resultant CBF variations), fever, hypoglycemia, hyperglycemia, even through the direct neurotoxic effect of pharmaceutical agents utilized (50). Tight control of these variable parameters to the extent possible is hence of utmost importance in the context of preventing secondary injury. This begins at the choice of anesthetic, with intravenous agents such as thiopental, propofol, and etomidate causing cerebral vasoconstriction (51). Volatile anesthetics (isoflurane, sevoflurane, desflurane) decrease the cerebral metabolic rate of oxygen and increase vasodilation, causing an increase in CBF and ICP. Nitrous oxide has a similar effect but comes at the added risk of

pneumocephalus or pneumothorax expansion. Some evidence points to propofol being the preferred sedating agent as it decreases cerebral metabolic demand and ICP and may even have neuroprotective effects as an in-vitro model has shown such promise (52) – on the other hand having associations with hyperkalemia, metabolic acidosis, rhabdomyolysis, and death (8). In developments of novel anesthetic agents, xenon has long been known to be an effective anesthetic (53,54) and is showing promising animal model results regarding neuroprotection. Specifically, an enhancement of microglial cell numbers and astrocyte activation – both playing a role in early beneficial neuroinflammation- in the end improving functional outcome, survival and reducing neuronal loss after brain trauma (55,56).

Hemodynamic management in patients with TBI has adequate cerebral blood flow as a primary goal. In healthy subjects, cerebral vasculature autoregulation maintains an adequate CBF across a wide range of hemodynamic states – this autoregulation is, however quick to become severely impaired, even in mild TBI (57). Thus TBI patients may become "pressure-passive", meaning a sudden rise in MAP may lead to secondary injury through pathologically elevated CBF and hyperemia. The inverse, too is true, with MAP drops leading to hypoperfusion and ischemia. Estimating CBF is not easy, with CPP being the most utilized approximation, as it can be calculated from the difference between MAP and ICP. Cerebral autoregulation is biased according to whether an individual has preexisting hypertension or not. The choice of fluid for resuscitation is another topic of research. Generally, crystalloid solutions appear superior to albumin (58), in select patients with risk of elevated ICP, hypertonic saline may be preferred– as studies show ambivalent results on its general usage (51). Another "space to watch" is whether TBI patients should have different packed red blood cell transfusion triggers than other critically ill patients, as there is a balance between injurious effects of anemia (e.g., ROS generation, inflammation, hypoxia) and the neuroprotective ones (e.g., direct hemodynamic and cellular protection mechanisms, including angiogenesis and vascular repair) (51).

One field of study showing recent promising results is that of utilizing mesenchymal stem cells. The underlying idea being their tendency to migrate to damaged tissue, crossing the BBB, with their ability to immunomodulate surrounding tissue, differentiate into neurons and glia, reducing local inflammation, promoting axon outgrowth, paracrine functions, direct cell-cell interactions, and various other pathways (15). Specifically, genetically modified mesenchymal stem cell-based

therapy may hold additional benefits, currently being investigated (59). This also holds promise regarding the prevention of the otherwise comparatively neglected syndrome of neurodegeneration after TBI.

Chronic neurodegeneration after TBI is characterized by progressive cognitive decline, psychiatric disorders, and cerebral atrophy. Sustained and together with the emergence of psychiatric disorders are they of major concern in the long-term sequelae management of TBI, with many symptoms overlapping other neurodegenerative disorders, both suggesting similar pathways of disease but also severely limiting the possibility of adequate monitoring/establishment of epidemiologic data. This is graphically represented in Figure 3. The similarity of pathological pathways becomes even more readily apparent when comparing the histological appearance of post-TBI/CTE brains with those of classical neurodegenerative diseases. Abnormal p-TAU, Aß Plaque formation, TDP-43 deposits, and α-synuclein deposits can all be encountered in brains post-TBI (60). Alzheimer's disease, Parkinsonism, and frontotemporal dementias all have TBI as a common risk factor, with mild and severe TBI increasing the risk for developing any dementia by 63% and by 51% for Alzheimer's disease (61). This is not to say these are the sole neurodegenerative diseases TBI is implicated in, nor that there are only a handful of pathological pathways branching out post-TBI. Rather the long-term sequelae of TBI are again to be considered both as an aspect of the disease itself but also as a sole heterogeneous disease to consider in its own context. This is represented in the vast body of research into post-TBI rehabilitation.

Post-TBI rehabilitation and the field of secondary injury preventing neuroprotection are a continuum, rather than two strictly separatable entities, with proposed therapies currently being researched, linking the two together. These novel therapies include but are not limited to stimulants, anticonvulsants, antipsychotics, and cellular therapies but are yet to be translated to broad clinical practice (5).

In recent times treatment of patients with severe TBI has become much more internationally standardized and broadly follows the Brain Trauma Foundation guidelines for management, often in specialized neurointensive care. Even so, the treatment given is focused around stabilizing the patient and mitigating their symptoms and complications. These guidelines were last updated in 2016 and are based upon existing evidence. Unfortunately, said evidence supporting several treatment concepts is relatively weak. Despite this, there is evidence that, broadly speaking,

treatment in high-volume neurosciences critical care units, which generally act according to these guidelines, is associated with better patient outcomes (62).

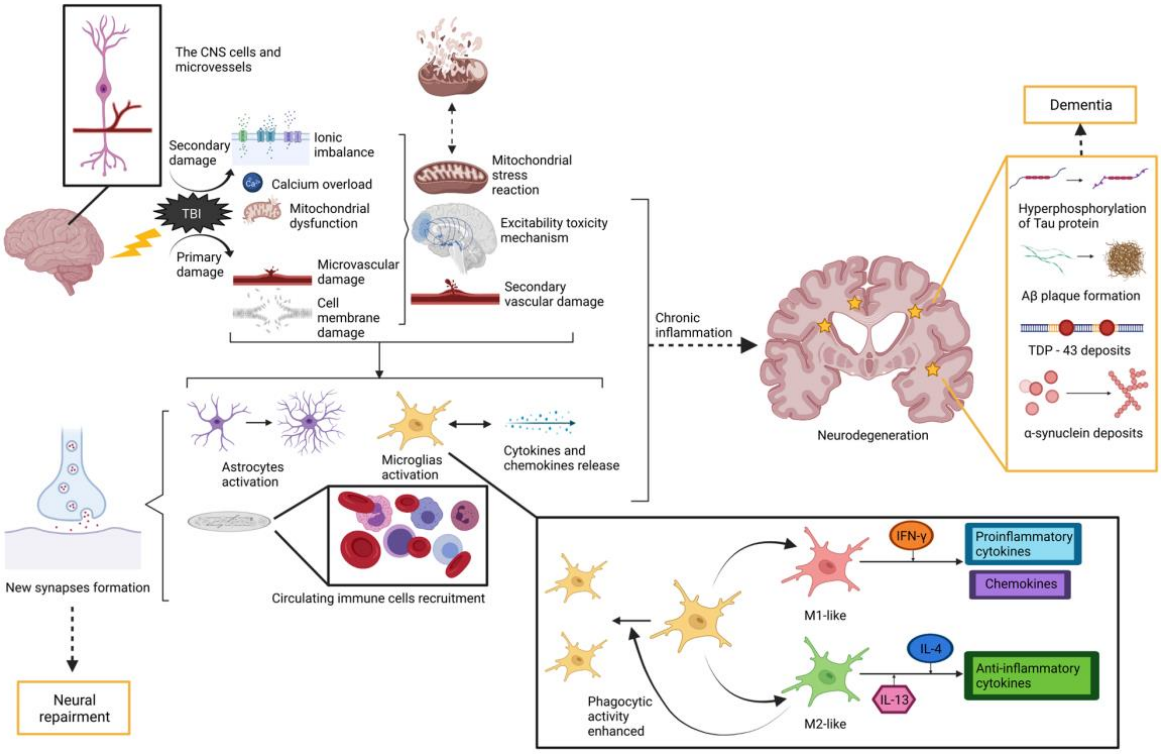

Fig. 3: Neuroinflammatory process after the occurrence of TBI and its consequences (60)

NEW POTENTIALLY ACTIONABLE DATA SINCE BRAIN TRAUMA FOUNDATION GUIDELINES FOR THE MANAGEMENT OF SEVERE TBI 4TH EDITION (2016)

Prophylaxis of PTS/Post-traumatic epilepsy in the setting of TBI. TBI patients have a fairly high incidence of PTS, especially in those with severe TBI, thus is given the rationale for routine seizure prophylaxis. Generally, Phenytoin is recommended (8) as pharmacologic agent, as at the time of guideline publishing, there was insufficient evidence to recommend levetiracetam over it. A meta-analysis concerning the early and late posttraumatic antiepileptic management has shown no difference in early seizure incidence between levetiracetam and phenytoin. Late PTS incidence appears unrelated to the usage of either antiepileptic, as neither showed benefit over the placebo. Given the comparatively advantageous side-effect profile of levetiracetam, it appears a prudent replacement (63).

The capacity of mitochondria to scavenge free radicals or reactive oxygen species appears at the center of inhibiting secondary injury through oxidative stress. One antioxidant used for this physiologically is glutathione, levels of which decrease rapidly after TBI (64). N-acetyl L-cysteine (NAC) replenishes glutathione synthesis, making it a candidate to ameliorate this type of secondary injury. NAC as a drug itself has a long clinical history, primarily used as a specific antidote for acetaminophen toxicity (65), but also finding usage in the prevention of chronic obstructive pulmonary disease exacerbation and contrast-induced kidney damage. More recent studies have shown its benefit in a related type of injury - cardiac injury and oxidative stress after abdominal aortic aneurysm repair (66). Its side effect profile includes effects such as nausea, vomiting, rash, and fever – rarely the more severe anaphylaxis. Limiting its application is its low blood-brain barrier permeability. This lack in BBB permeation has been addressed with the drugs amide derivative – N-acetylcysteine amide – which crosses it more easily, although cerebral injury sites post-TBI present an injured and permeable BBB, making it credible for the classical form of NAC to have a tangible effect. This appears to be reflected in data, with a study examining the role of NAC substitution in U.S. Service members within 0-72 hours after blast exposure showing a much higher rate of symptom resolution than placebo (67). A more recent systematic review of animal and human studies demonstrated moderate-quality evidence of efficacy and safety concerning the use of both NAC and its amide form in pre-clinical studies but still points to a lack of more concrete data and the necessity of further study (32). There is no mention of ROS mitigation in the BTF guidelines.

Another highly promising approach to treating TBI is the utilization of hyperbaric oxygen therapy (HBO). The underlying mechanisms altering TBI prognosis are speculated to be multifaceted, with the potentials being a reduction in tumor necrosis factor-α-mediated inflammation, leading to better vascular recovery. A presumed pathological mechanism in TBI is an elevation in ICP leading to microcirculatory injury, which in turn leads to an increase in injury, presenting a cycle. The increased oxygen delivery during HBO offers the possibility to break through this cycle in areas. Improved oxygen supply also promotes vasoconstriction and vascular regeneration, thus further promoting the recovery of vulnerable tissue (68). A phase I study on military personnel suffering from chronic blast-induced mild to moderate TBI has shown improvement in symptoms, physical exam findings, cognitive testing, quality-of-life measurements, as well as diffuse improvements in regional cerebral blood flow on SPECT mapping (69). It is to be considered that

military and civilian TBI may present differently. A separate randomized trial was done on presumably civilian subjects in the setting of severe TBI, with control and experimental groups being n=44, receiving HBO approximately 1 week after admission. Results showed the experimental group with higher GCS and lower National Institutes of Health Stroke Scale scores. This makes HBO another potential treatment to improve cognitive function and prognosis (68).

TBI patients have a fairly high likelihood of developing intracranial bleeding soon after impact, which in turn comes with their typical risk of precipitating secondary injury, increased ICP, cerebral herniation, and death. Tranexamic acid has a long history of usage to decrease risk of death by bleeding in surgical patients, giving rise to the idea of it having a benefit in TBI patients. The CRASH-3 trial (70) was a recently finished international, multi-center, randomized, placebo-controlled trial with N=12 737 (of which 9202 received treatment within 3 h of injury), researching the value of administering 1 g of tranexamic acid intravenously over 10 minutes and another 1g over 8 hours (70). Only those patients with uncertainty about the appropriateness of tranexamic acid treatment were included, and those with a GCS score of 3 or bilateral unreactive pupils before treatment were excluded as their inclusion would bias treatment effect, as most of these patients already have extensive intracranial hemorrhage and its sequelae, hardly mediatable by tranexamic acid. Results found a reduction in the risk of head injury-related death in patients with a mild-to-moderate head injury but no such reduction in those with a severe head injury. As hemorrhage expansion occurs within hours of primary injury, time is of the essence when administering tranexamic acid. The 3-hour time frame was utilized in this study, with the prior CRASH-2 trial showing the greatest benefit of treatment on the day of the injury with attenuated effect thereafter. There was no evidence of increased adverse event risk. Deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction risk were similar in the tranexamic acid vs. placebo group. This trial provides evidence of tranexamic acid safety and benefits against mortality in the treatment of patients with mild to moderate TBI within 3 hours of injury, used as soon as possible (70). There is no mention of tranexamic acid in the BTF 2016 guidelines.

CONCLUSIONS

Neuroprotective measures targeting key mechanisms involved in the initiation and propagation of secondary injury are hardly, if ever, concerned in present guidelines, with them being focused around symptomatic and parameter-based treatment, such as maintaining cerebral blood flow, and

controlling intracerebral pressure, preventing cerebral hernia and homeostasis derailment. This holds value in the treatment of the disease, as the alternatives are highly injurious complications. Given the very high morbidity and mortality of this disease, more individualized and disease-specific treatment is desirable. Active neuroprotection at the micro-level appears to be one gateway to increasing both short- and long-term outcomes for this patient population.

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