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Traumatic brain injury: neuropathological, neurocognitive and neurobehavioral sequelae

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Abstract
Traumatic brain injury (TBI) causes substantial neurological disabilities and mental distress. Annual TBI incidence is in magnitude of millions, making it a global health challenge. Categorization of TBI into severe, moderate and mild by scores on the Glasgow coma scale (GCS) is based on clinical grounds and standard brain imaging (CT). Recent research focused on repeated mild TBI (sport and non-sport concussions) suggests that a considerable number of patients have long-term disabling neurocognitive and neurobehavioral sequelae. These relate to subtle neuronal injury (diffuse axonal injury) visible only by using advanced neuroimaging distinguishing microstructural tissue damage. With advanced MRI protocols better characterization of TBI is achievable. Diffusion tensor imaging (DTI) visualizes white matter pathology, susceptibility weight imaging (SWI) detects microscopic bleeding while functional magnetic resonance imaging (fMRI) provides closer understanding of cognitive disorders etc. However, advanced imaging is still not integrated in the clinical care of patients with TBI. Patients with chronic TBI may experience many somatic disorders, cognitive disturbances and mental complaints. The underlying pathophysiological mechanisms occurring in TBI are complex, brain injuries are highly heterogeneous and include neuroendocrine dysfunctions. Post-traumatic neuroendocrine dysfunctions received attention since the year 2000. Occurrence of TBI-related hypopituitarism does not correlate to severity of the GCS scores. Complete or partial hypopituitarism (isolated growth hormone (GH) deficiency as most frequent) may occur after mild TBI equally as after moderate-to-severe TBI. Many symptoms of hypopituitarism overlap with symptoms occurring in patients with chronic TBI, i.e. they have lower scores on neuropsychological examinations (cognitive disability) and have more symptoms of mental distress (depression and fatigue). The great challenges for the endocrinologist are: (1) detection of hypopituitarism in patients with TBI prospectively (in the acute phase and months to years after TBI), (2) assessment of the extent of cognitive impairment at baseline, and (3) monitoring of treatment effects (alteration of cognitive functioning and mental distress with hormone replacement therapy). Only few studies recently suggest that with growth hormone (rhGH) replacement in patients with chronic TBI and with abnormal GH secretion, cognitive performance may not change while symptoms related to depression and fatigue improve. Stagnation in post-TBI rehabilitation progress is recommended as a signal for clinical suspicion of neuroendocrine dysfunction. This remains a challenging area for more research.

Keywords Traumatic brain injury · Mild TBI · Neuropathology · Cognitive deficits · Behavioral dysfunction

Introduction

Numerous studies have raised the awareness, improved diagnostic classification, management and prognosis of traumatic brain injury (TBI) of all degrees of severity. However the underlying pathophysiology is only partially understood, in particular for mild traumatic brain injury (mTBI) and sports-related concussion. The aim of the current review is to summarize contemporary areas of active research such as difficulties in defining different subtypes of mild TBI and recent data on chronic traumatic encephalopathy. The

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aim is also to provide an overview on the improvements in neuroimaging, biomarkers, genetics and biomechanics leading to improved understanding of injury epidemiology, management challenges and TBI outcome. In particular this review will summarize available data on the effect of hypopituitarism (in particular GH deficiency) following TBI on neurocognitive and neurobehavioral functions and the effect of rhGH replacement on these changes.

Definition and classification of TBI

Traumatic brain injury (TBI) is defined as alteration in brain function, or other evidence of brain pathology, caused by an external force. Presence of one of the following signs is required: loss of or impaired consciousness, memory loss for events prior or after the injury, neurologic deficits (weakness, loss of balance, altered vision etc.) or mental disturbances confusion, disorientation, slow thinking etc [1–3].

Standardized definition for mild TBI (mTBI) is currently lacking. The US Centers for Disease Control and Prevention (CDC) defined mTBI as "any period of observed or self-reported: transient confusion, disorientation, or impaired consciousness; dysfunction of memory around the time of injury; loss of consciousness lasting less than 30 min" as well as "observed signs of neurological or neuropsychological dysfunction" [4]. The most widely accepted criteria for mTBI are: blunt trauma, Glasgow coma scale of 13–15, brief loss of consciousness(< 30 min), and brief posttraumatic amnesia(< 24 h) [5, 6]. Mild TBI is not expected to be associated with abnormalities on computed tomography (CT). However, patients may endure prolonged cognitive, emotional and functional disabilities, with significant impact on quality of life. Increased awareness in the past decade originated from observations of chronic outcome of mild cases of TBI (concussion) in professional athletes and military combat personnel [3].

The main classification discriminates closed (blunt) and open/penetrating TBI according to intactness or penetration of dura mater and skull [7, 8]. Penetrating injuries are synonymous with severe TBI. This review hereby focuses on closed non-penetrating TBI.

TBI severity ranges from mild TBI (concussion) to moderate and severe. Clinical severity is determined with Glasgow coma scale (GCS, Fig. 1). GCS of 13–15 defines mild TBI with full neurological recovery, moderate TBI with GCS of 9–12 when the patient has decreased level of consciousness and severe TBI with GCS of 3–8 with coma. Approximately 75–90% of TBI are classified as mild TBI [9].

Classification of clinical severity of TBI on the basis of the level of consciousness in GCS is a relatively crude tool which may not adequately capture the gravity of TBI. GCS does not reflect different pathoanatomical subsets of TBI. Correct GCS assessment is often confounded by pre-hospital sedation and tracheal intubation [10]. Concussions and mild traumatic brain injury (mTBI) contribute substantially to the annual TBI incidence. The reporting of concussions in

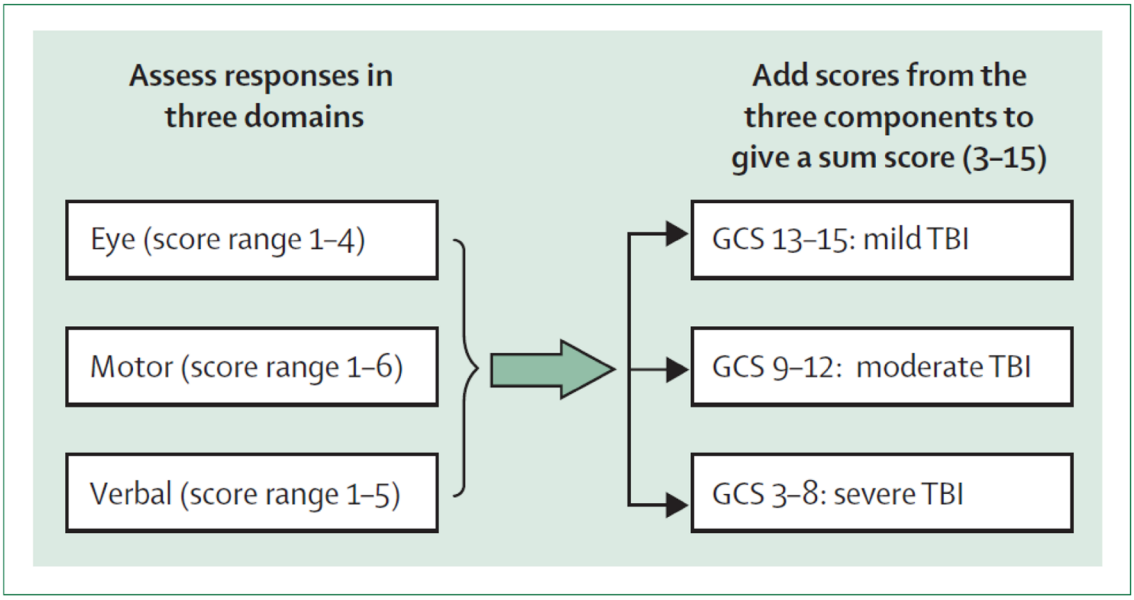

Fig. 1 Classification of clinical severity of traumatic brain injury with the Glasgow Coma Scale. Responses are assessed in three domains (eye, motor, and verbal) and individual scores are added to give a Glasgow Coma Scale (GCS) sum score for mild, moderate, or severe traumatic brain injury (TBI). "Reprinted from *Lancet Neurol*, 16(12), Maas AIR et al., Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research, page 991, Copyright (2017), with permission from Elsevier"

athletic and in military setting (blast injuries) is increased. Repetitive mild head injuries, particularly in recovery period after previous injury, induce long-term white matter pathology and neuronal loss, which correlate with behavioral deficits [11]. Thus long-term sequelae of repeated mild TBI may resemble changes recognized in moderate and severe injuries (cumulative effect of subsequent mild TBI).

Furthermore, wide variations in the clinical manifestations of TBI are attributable to the cerebral complexity and other factors. The pattern and extent of damage depend on site of impact and cranial architecture, direction and duration of the external TBI-causing forces, but also on the host tolerance of head impacts (e.g. biomechanical studies in sports-related concussion) and other known or suspected confounding and modifying factors (e.g. genetics, childhood adversity, personality factors, family mental health history, drug and alcohol abuse, opioid and steroid use, chronic pain, depression, anxiety, life stress, marital and family problems, and general medical health) [12]. Angular and linear head acceleration linked to clinically confirmed sports-related concussion displayed sizable individual variation [13].

Epidemiology

TBI can be designated as a 'silent epidemic' owing to high incidence and prevalence but insufficient publicity [2]. The epidemiology of TBI is evolving. In the aging population of high-income countries the prevalence of elderly with TBI is increasing mainly due to falls, while in developing countries traffic-incident related injuries mainly contribute to increase in TBI prevalence [10]. Armed conflicts are now characterized worldwide with the historically lowest killed-to-wounded ratio. Professional sports are focusing on heavier and stronger physical contact [10]. The incidence of TBI related hospital admissions in Europe is estimated as 262 per 100,000 TBI [2]. The TBI related annual mortality rate in Europe was estimated to 15 per 100,000 [14]. Many patients with mild TBI never seek medical assistance or they are treated by general practitioners. Thus the true incidence and prevalence of mild TBI is probably underestimated [15] Substantially higher incidence rates for TBI are found in population based studies with broad definitions of TBI (811–979 per 100,000 people per year) [16–18] than in studies based on hospital discharge rates (475–6435 per 100,000 people per year) [18, 19].

TBI in specific situations

Concussions are a occurring frequently in contact sports such as football, hockey, lacrosse, and soccer. Accumulating evidence indicates that athletes may endure multiple concussions throughout their career [13, 20–22]. Active military personnel is at risk of suffering from combat-related TBI, including blast-injuries. One in six soldiers returning from combat deployment in Iraq was diagnosed with concussion [23]. Increasing risk of repeated TBI among younger children resembles the pattern seen for first-time injuries. Abusive trauma is the most common cause of TBI in infants. TBI in the elderly appears as a risk factor for repeated incident TBI. A possible bimodal distribution of repeated TBI is likely, concentrating the risk in younger children and older adults, but further investigation is warranted [23]. A bidirectional epidemiologic relationship binds TBI and crime offenders. Violence often results in TBI, but additionally TBI survivors may experience psycho-social impairments possibly resulting in risk-taking or criminal behavior [10, 24].

Characterization of TBI

TBI is not only a single pathophysiological phenomenon, but rather a complex disease process generating structural and functional damage from both primary and secondary injury mechanisms [25]. Primary damage is inflicted at the time of injury, and secondary damage evolves over hours, days, weeks, months or even over lifetime. Following TBI, brain lesions are not limited to the site of the primary trauma, but expand progressively and centrifugally. Secondary damage is prompted by host responses to primary injury.

The primary injury results from the immediate mechanical disruption of brain tissue occurring simultaneously to exposure to the external force. It incorporates contusion, blood vessels damage, hemorrhage, and axonal shearing, in which neuronal axons are stretched and wavering [26, 27]. Secondary injury develops over minutes to months after the primary injury and originates in cascade of metabolic, cellular, and molecular events leading ultimately to brain cell death, tissue damage, and atrophy [28].

Improvements in the characterization of TBI

Progress in TBI characterization is established by: (1) biomechanical studies (quantifying direct or indirect force(s) to the brain), (2) use of advanced neuroimaging for identification of underlying functional disturbance and structural injury (3) employment of blood/CSF biomarkers and (4) genetic analysis.

The complexity of impact biomechanics and TBI risk

Biomechanical studies reveal that sport-related concussions are caused by impacts less severe than those causing cranial

fractures, intracranial hemorrhages or diffuse axonal injury [28]. Investigation of concussive events in contact/collision sports demonstrate different regional cerebral effects depending on the impact characteristics: mass, velocity, exposure duration and frequency, location of direct or indirect external mechanical forces, interplay of head kinematic responses, brain geometry and various intracranial tissues properties, skull architecture, as well as individual tolerance to head impacts (energy status, prior concussions and genetics). These various impact characteristics contribute to a combination of linear and rotational accelerations which leads to neuronal structure alteration, in the absence of macroscopic damage in contact/collision sports [29]. The impact magnitude (lower- energy magnitudes), higher frequency, shorter inter-impact intervals (repeated trauma) and duration of trauma exposure (continuous exposure without compensatory recovery), have cumulative effects on brain vulnerability [29]. High linear accelerations causing pressure gradients and skull deformities are mainly responsible for focal brain injuries in coup/countercoup pattern. However, diffuse brain injury is caused mainly by rotational acceleration causing shear stress due to differential motion between skull and brain. Traditional methods using symptom based assessment and diagnostic tools lack sensitivity to capture high tissue stress and strains in concussive and sub-concussive brain trauma. Magnitude alone does not capture full risk profile of brain injury or long term consequences of repetitive head impacts. Repetitive brain trauma of lower magnitude may result in similar pathologic outcomes as a single severe event [29]. Thresholds for identifying an injury and quantifying its impact are poorly defined [12].

Neuroimaging

CT is the primary imaging modality for patients with TBI, although it lacks sensitivity for detecting deep cerebral lesions and may omit up to 30% of cerebral abnormalities detected by other methods [30]. Although CT is superior for evaluation of skull fracture, the sensitivity of MRI is significantly higher for detection of contusion, shearing injury, subdural and epidural hematoma, and sinus involvement (sensitivity 96.4% for MRI and 63.4% for CT) [30–33]. Emerging technologies that can improve disease characterization and prognosis, such as MRI, are not yet fully integrated in the TBI clinical care.

The role of advanced neuroimaging techniques that quantify potential network-level damage using Diffusion tensor imaging (DTI), susceptibility weighted imaging (SWI) and resting state functional MRI (fMRI) are used to distinguish the underlying subtle neuropathology in mild TBI. Advanced MRI (DTI and SWI) enables dissection of pathophysiological mechanisms of mild TBI since DTI is sensitive to map axonal injury by detecting change in water micro compartments due to microstructural pathology as axonal deformation and swelling (Fig. 2).

Diffusion tensor imaging (DTI) is an MRI protocol that determines fiber connections degree between the brain hemispheres and from the frontal to the occipital brain region. Focal microscopic bleeds developing as component of diffusion axonal injury are most successfully detectable by SWI, a method exploiting the magnetic property of iron. Presence of microbleeds detected by SWI was associated with worse cognitive outcome and persistent post-concussion syndrome in mild TBI patients, while DTI was not predictive of neuropsychological outcome in the acute phase [34].

Other advanced MRI studies include MR spectroscopy (MRS) and functional MRI (fMRI). MRS elucidated bran metabolic state in vivo. fMRI investigates the effect of TBI on some brain functions including perception or cognitive tasks-memory and concentration [31].

Neuropathology and blood biomarkers in TBI

A range of pathological changes diversely contribute to distinct clinical pictures in individual patients. The leading pathological substrates are diffuse axonal injury (DAI) and contusions (cortical) in diverse ratios. Blunt TBI mechanism frequently consists of rotation and acceleration with diffuse stretching and shearing of both axons and vascular components with increased permeability. Predilection areas for DAI are deep parasagittal white matter, internal capsule, corpus callosum, fornix and upper brain stem. Focal hemorrhagic contusions have preference sights in the frontal and temporal lobes. These processes induce excitotoxicity, apoptosis, inflammation, demyelination, white matter pathology, and decreased neurogenesis [28]. These are pathophysiologic mechanisms involved in the acute and long-term consequences of TBI. Ischemia and inflammatory responses and amyloid deposition associated with neurodegeneration after repeated TBI (unrecovered concussions) can result in chronic brain injury syndrome which is designated in the literature as chronic traumatic encephalopathy—CTE [35].

Traumatic brain injury (TBI) also affects structures distal to the cortical injury namely in the hypothalamus and the pituitary. The involvement of these structures, remote from injury sites in posttraumatic alterations is intriguing. At the anatomical level, some but not all patients show pituitary stalk and/or gland lesions, and hypothalamic lesions can be found in the absence of pituitary affliction. Animal study in which cortical injury induced chronic GH deficiency suggests that systemic inflammation and persistent astrocytosis in the hypothalamus and anterior pituitary may be the possible cause of hypopituitarism [36]. Another mechanism recently established is that the barrier properties of the third ventricle tanycytes are compromised in a murine model of cortical injury. Tanycytes are specialized ependymal cells

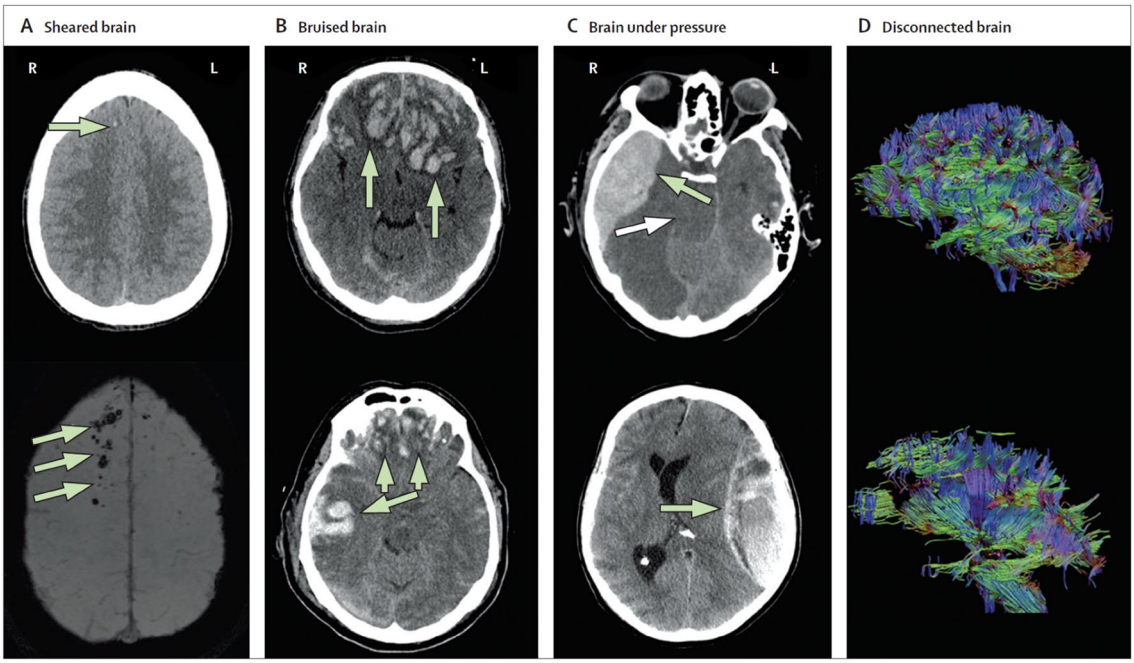

Fig. 2 The multiple faces of traumatic brain injury. **a** Sheared brain: the typical picture of axonal injury on computed tomography (CT; upper panel) and magnetic resonance imaging (MRI) using susceptibility-weighted imaging (lower panel) in an adult patient with traumatic brain injury (TBI). Note the greater sensitivity of MRI for detection of microbleeds (green arrows), which are commonly associated with diffuse axonal injury. **b** Bruised brain: contusional brain injury (green arrows) on CT in two elderly patients with TBI, typically located in the frontal and temporal regions. **c** Brain under pressure: a typical epidural haematoma (bleeding between the skull and outer coverings of the brain; green arrows) on CT in two adult patients with TBI. The haematoma in the upper panel is an example of an injury that compresses the brainstem (white arrow); the haematoma in the lower panel causes midline shift and indirect compression of the brainstem due to raised intracranial pressure. Both are life-threatening and constitute a neurosurgical emergency. Patients can recover completely if operated on quickly. **d** Disconnected brain: white matter tracts measured with diffusion tensor imaging and visualised by MR tractography in an adult patient with TBI 12 days after the injury (upper panel) and at 6-month follow-up (lower panel). Note the extensive progressive late white matter loss. "Reprinted from *Lancet Neurol*, 16(12), Maas AIR et al., Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research, page 989, Copyright (2017), with permission from Elsevier"

lining the floor and basolateral walls of 3rd ventricle preventing portal substances from entry into brain. TBI-induced disruption of 3rd ventricle tight junctions at the median eminence (EM) may be associated with consequent tanycyte dysfunction dampening GH pulsatility. The underlying pathology of hypopituitarism in this model of TBI lies in the hypothalamus with intact pituitary gland and stalk [37].

Host neuronal and glial proteins are released into the vascular and cerebrospinal fluid compartments following TBI. Acute phase TBI blood biomarker most commonly used in children and adults is S100 astroglial calcium-binding protein β(S-100β) [38, 39]. Serum S-100β concentrations correlate significantly with unfavorable prognosis in patients with moderate or severe TBI, as defined by mortality, Glasgow outcome score ≤ 3, or brain stem death [40]. Recommended sampling time is within 3 h of trauma. This biomarker is used also in acute phase of mild TBI to stratify patients as candidates for CT imaging. Using negative S-100β as an indicator for discharging a TBI patient without a CT scan could reduce the need for CT scan by 30% [38]. Further research is needed to establish the prognostic value of S-100β protein for persistent post-concussion symptoms in mild TBI [41]. The search is ongoing for novel classes of biomarkers to improve definition of abnormalities reflecting the underlying physiological disruption or injury (microRNA, exosomes, glial fibrillary acidic protein—GFAP, microtubule-associated protein (MAP), tau and phosphorylated tau, neuron-specific enolase (NSE), myelin basic protein (MBP), spectrin, amyloid β peptideAβ42 etc) [42, 43] (Fig. 3). The neural proteins are generally detected between 4 and 72 h post TBI with a peak occurring within 24 to 48 h [42]. Biomarkers levels are elevated for up to 90 days after TBI and correlate with clinical and radiological variables of TBI severity (total tau levels) and with clinical outcome (plasma Aβ42) [43]. The release of these brain proteins into the vascular compartments through compromised blood-brain barrier (BBB), may induce an autoimmune response and production of antibodies against neuronal and glial proteins (anti-GFAP, anti neurofilament, anti-S100β). Some of obstacles in the use of biomarkers lay in the complex

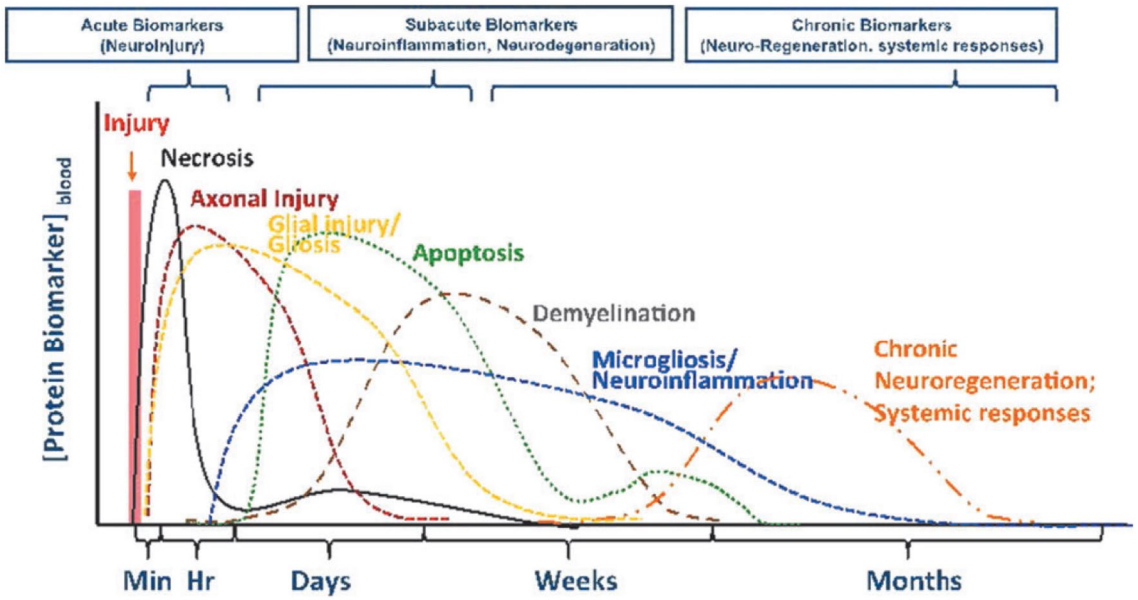

Fig. 3 Continuum of biomarkers for TBI pathophysiology and its manifestation over time. Reprinted from Bramlett et al., Long-term consequences of traumatic brain injury: current status of potential mechanisms of injury and neurological outcomes. J Neurotrauma. 2015; 32(23): 1834–1848. with permission from Journal of Neurotrauma, Copyright © 2015, Mary Ann Liebert, Inc

transport from damaged cerebral tissue to circulation and potential discrepancy of the sometimes small size of the lesion (resulting in a small biomarker footprint) but paramount functional importance of the involved cerebral region [10].

Genetics and TBI

TBI induces an immune response with focal and peripherally-derived cellular and humoral mechanisms. These complex TBI-induced immune responses are initiated acutely (within minutes after injury) and may be protective (brain-blood barrier preservation, debris clearance, inflammation resolution, and the release of trophic factors), but also can persist for decades causing a chronic inflammatory disorder (chronic traumatic encephalopathy, CTE). The functional and cognitive outcome after TBI is highly variable and this may be influenced by interindividual genetic variability and epigenetic mechanisms in injury (Fig. 4). Genomics of the host response may modulate injury course (pro- and anti-inflammatory cytokines, calcium signaling, apoptosis, vascular response) as well as repair and plasticity (neurotrophic genes) and may affect pre- and post injury cognitive and neurobehavioral capacity (catecholamine genes) [44]. Systematic review of studies evaluating the association of genetics with recovery after TBI and system biology-based approaches (computational analysis) suggest that a number of genes may affect TBI-induced injury and recovery [45].

Most extensively studied gene is the apolipoprotein E (APOE) involved in lipid metabolism in the brain. The precise relation between APOE genotype and TBI outcome remains uncertain. Other genetic polymorphisms within neuroinflammatory mediators associated with TBI include: tumor necrosis factor α (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), transforming growth factor-β (TGF-β), APO promoter, microtubule-associated protein tau (MAPT), catechol-O-methyltransferase (COMT) gene, angiotensin-converting enzyme (ACE) and brain-derived growth factor (BDNF) gene polymorphisms [44]. The study of mitochondrial genomic variants on TBI outcome is still in its early stages.

MicroRNAs (a class of small non-coding RNA molecules) in the hippocampus and cerebral cortex may regulate the expression of numerous human genes and play also an important role in TBI [46]. MicroRNAs are instrumental for formation of neural network, neural genesis and differentiation. TBI is reported to alter microRNAs levels in brain tissue, blood and CSF possibly affecting brain recovery [46].

Genetic variations involved in brain functions may also affect pharmacotherapy for TBI. Pharmacogenomics use the knowledge of genomics to tailor therapeutics associated with acute and chronic care of TBI patients [47]. Studies on genetic variations in blood-brain barrier (BBB) transporters or drugs (phenytoin, propofol, midazolam, ketamine, morphine, antidepressants) pharmacokinetics and response (CYP2C9, CYP3A4/5, HLA-B, etc.)

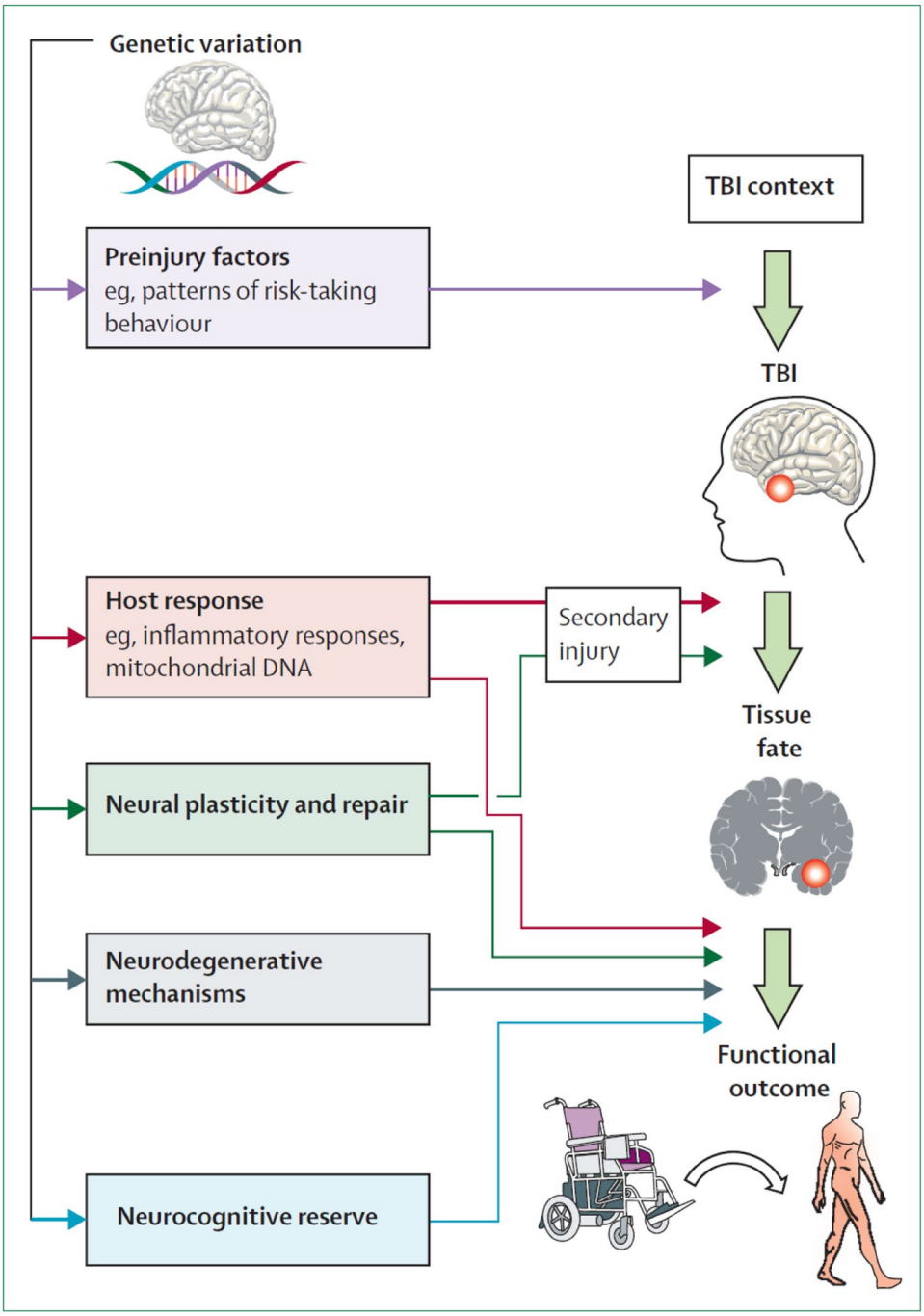

Fig. 4 Potential effects of genetic variation on clinical course andoutcome of traumatic brain injury. Genetic factors might influence an individual's risk of and response to traumaticbrain injury (TBI), contributing to functional outcomes in the short and longerterm. Although still speculative, possible applications of such knowledge couldinclude use of genetic factors that might modulate TBI outcome (e.g. apolipoprotein E [APOE] genotype) in a comprehensive prognostic scheme, orstratification of patients for clinical trials of treatments on the basis of genotypesthat modulate the host response (e.g. proinflammatory response), influenceregenerative capacity (e.g. brain-derived neurotrophic factor [BDNF]concentrations), or affect mitochondrial biology. "Reprinted from *Lancet Neurol*, 16(12), Maas AIR et al., Traumatic brain injury: integrated approaches to improve prevention, clinical care, and research, page 1015, Copyright (2017), with permission from Elsevier"

revealed association of certain genotypes with different TBI outcomes or drug responses [47].

Further analysis are required of the correlation of HLA subtypes/MHC class II and susceptibility/vulnerability of the host to manifest autoimmune response to TBI, as well pharmacogenomics.

TBI outcome

TBI outcome can be analyzed as acute and chronic (long-term outcome). Some symptoms and signs resolve within 2 weeks but some are persistent.

A range of evolving clinical symptoms and signs include alteration in physical, cognitive (e.g. confusion, disorientation, slowed thinking) and affective (e.g. emotional) symptoms that may or may not involve transient loss of consciousness [15, 48].

Common physical symptoms associated with TBI are headache, dizziness/nausea, fatigue or lethargy, and sleep pattern alterations [15, 48]. Headache is the most frequently reported physical symptom following mild TBI and is considered acute if it resolves within 2 months or chronic if it persists for longer than 2 months. Dizziness is another common symptom of TBI and generally resolves within 2 months but may continue in patients with moderate or severe TBI [15, 49]. Another particularly debilitating symptom is fatigue, likely originating from difficulty in initiating or maintaining sleep. The brain injury complaint questionnaire (BICoQ) has recently been developed with 25 questions in the domains of: cognition, behavior, fatigue, sleep, mood and somatic problems. The most frequent complaints were mental slowness, impaired memory, fatigue, concentration difficulties, anxiety and dual tasking problems [50].

Adverse neuropsychological outcome that includes disturbances of attention and memory, slow cognition, inability to carry on multitasking, increased distractibility, and mild confusion particularly in patients with mild TBI is designated as post-concussion syndrome (PCS) [15, 51, 52]. Symptoms in most cases resolve in 1 to 2 weeks but cognitive impairments might last for 1 to 3 months post injury [51, 53]. Prolonged cognitive complaints are observed in about 15% of patients after 1 year [3].

Cognitive deficits are characterized by impaired attention, memory, and/or executive functions and may cause irritability, anxiety, or depression. Cognitive deficits in cases of mild TBI generally resolve within days. Older patients were more cognitively impaired. Cognitive sequelae were present most often in the domains of arousal, attention, concentration, learning, memory, conceptual thinking, problem solving, and language [54]. Age related decline in cognitive reserve may unmask the consequences of previous TBI [10].

Additional assessment may require neuropsychological testing which reveals problems on tasks of complex conceptual tracking, attention span, free recall, nomination impairment, sometimes with verbal paraphasia.

Studies since year 2000 confirm that TBI is a risk factor for hypopituitarism. Complete or partial hypopituitarism may develop as a consequence of TBI equally in patients with mild or those with moderate-to-severe TBI. Symptoms encountered in patients with chronic TBI may overlap with symptoms of hypopituitarism. Hypopituitary patients demonstrate impaired memory performance, lower scores on neuropsychological tests and increase in mental distress symptoms [55, 56]. We and others have observed different patterns of deficits across the neuropsychological tests in patients with TBI induced hypopituitarism [57]. Many animal and human studies have reported a possible relation between GH deficiency (GHD) and cognitive impairment [58–61]. Animal studies data suggest that early onset of GHD reflects negatively on learning and memory in midlife and could be prevented by GH supplementation [61]. In accord with these animal studies are recent findings in short children with GHD in whom replacement with rhGH improved cognitive function [62]. Contrary to previous studies we did not find any significant differences in tested cognitive variables between GH sufficient and GHD post-traumatic patients [54]. These differences could be related to many factors including age at TBI-related neuroendocrine dysfunction and extent of cognitive impairment at baseline. In patients with hypopituitarism, GH replacement causes changes in the CSF neurotransmitter levels, improvement in well being and cognitive function [59, 63–68]. GH is the most sensitive anterior pituitary hormone that frequently becomes deficient in patients with TBI. While in some studies treatment with rhGH improved cognition and quality of life in TBI patients who have GHD in others, rhGH treatment did not change cognitive functioning but patients were less depressed and had less fatigue [57, 69, 70]. Beneficial effects of rhGH on cognition remain to be better defined taking into account age, rhGH dose and the extent of baseline cognitive impairment.

Behavioral (psychiatric) manifestations following TBI include personality changes, depression, and anxiety, impulsivity, irritability, emotional lability, and apathy. TBI patients reached higher symptom scores in dimensions concerning depression and anxiety. Major depression is one of the most frequently reported behavioral sequelae of TBI, accounting or approximately 25–40% of cases of moderate-to-severe TBI [48]. In our study, patients with hypopituitarism following TBI had similar psychiatric manifestations as TBI patients with normal pituitary function [57] In our follow-up study we investigated the effects of replacement therapy with rhGH for a period of 1 year in six GHD post-traumatic patients. We recorded significant improvement in psychiatric functioning. GH replacement decreased the severity of depression, anxiety, intensity of interpersonal sensitivity and paranoid ideation [57, 71, 72].

In summary, many somatic, cognitive, and affective symptoms following mild TBI interact with and exacerbate each other. Some may be risk factors for experiencing another TBI.

Long-term outcome of TBI-neurological disability

TBI confers a long-term risk for cognitive impairment and dementia, stroke, parkinsonism and epilepsy. Importantly, TBI is a modifiable risk factor for these conditions. These risks also occur in milder forms of TBI especially after

repetitive injuries. Since mild TBI make the largest contribution to all of TBI, this category has an important healthcare impact. TBI is often a progressive disease with long-term consequences. Long term follow up reveals in up to 50% of TBI patients deterioration visible on advanced neuroimaging. Risk factors for prolonged complaints are female sex, litigation, low socio-economical status, previous TBI, depression and anxiety prior to injury, genetic factors, substance abuse and extra-cranial injuries [15].

Chronic traumatic encephalopathy: *dementia pugilistica*

Exposure of athletes to the risk of multiple mTBIs is greater than in general population. The cumulative effects of these events showed conflicting results in different studies [51]. The issue of long term neuropathological consequences of TBI in professional athletes remains in focus of a longstanding and ongoing debate. Chronic traumatic encephalopathy (CTE), was initially designated as *dementia pugilistica* or punch drunk disease in boxers in the first half of twentieth century. It was described in athletes active or retired from professional career in a range of contact, collision or combat sports—most popularly associated with American football and boxing, but also martial arts, soccer, ice hockey and others. Non-sport related CTE is recognized after combat related brain injuries in young active military personnel and retired veterans [73–75].

CTE is believed to represent a chronic and progressive neurodegenerative primary tauopathy developing insidiously after exposure to single, episodic or repetitive head trauma, including mild injuries, and leading to dementia or depression. Its hallmark is build up of hyperphosphorylated tau (p-tau) protein (and other pathological proteins, such as Amyloid β, α-synuclein and TDP-43) as neurofibrillary tangles, abnormal neurits and perivascular astrocyte inclusions. The topographic distribution (predilection for depths of sulci) and extent delineate CTE from other tauopathies—mainly Alzheimer`s disease (AD) and primary age related tauopathy [76]. The etiopathogenetic cascade of CTE includes: axonal injury resulting from head impact, leading to chronic neuroinflammation, and decreased neuroregeneration in the setting of prolonged or repetitive TBI (particularly in context of an inadequate recovery from prior TBI events) leading to tau pathology [77]. Chronic inflammation involving active microglia and cytoskeletal abnormalities leads to widespread blood-brain barrier disruption [74]. Tau acetylation is believed to be the initiating event leading to a vicious circle of repetitive damage and imperfect repair, with tau phosphorylation as the "second hit" in the succession of events resulting in p-tau aggregation and microtubule destabilization [75, 78].

The latency period in the course of CTE development corresponds to tau propagation from focal to widespread areas as a consequence of progressive axonal disruption, and possibly prion-like propagation [75]. This window of dormancy is particularly important in the view of the untreatable yet preventable nature of CTE focusing on the prevention of exacerbation of injury and prevention of subsequent TBI event principally in the recovery period [75].

CTE is currently a pathological diagnosis only. A preliminary consensus was established for pathologic criteria for diagnosis and severity stratification [79]. On the other hand, the clinical diagnosis of CTE and ante mortem prediction remain challenging [77]. CTE is expressed as three common syndromes: a behavior-predominant, mood-predominant and parkinsonism [75, 80]. CTE usually begins in mid-life with a neurological signs including: dysarthria, intentional tremor, pyramidal, cerebellar and extrapyramidal signs, epilepsy and parkinsonism, emotional and cognitive dysfunctions [81, 82]. The young onset CTE is initially characterized by behavioral and mood alterations progressing to cognitive impairment, while in the older age onset CTE presents with cognitive derangements such as episodic memory and executive function impairments [77]. Early symptomatic period is often associated with substance abuse and suicide risk, while parkinsonian-like motoric alterations are a possible late stage manifestation [75]. Motor-neuron disease (MND) is rarely present [83]. Cognition is characterized by slow thought, memory problems, behavioral changes, euphoria, emotional lability, dementia, delusions, rage attacks, aggressiveness and indifference for the surroundings [81].

Establishment of imaging or biomarker criteria for in vivo clinical diagnosis of CTE and risk assessment is focus of intensive research. F-18 FDDNP PET is a promising method for in vivo assessment of brain trauma, correlating well with postmortem findings [84]. PET based measurement of glial activation was investigated as indicator of focal brain injury and repair [85]. MR spectroscopy is hoped to be used as a "virtual biopsy" tool to diagnose CTE [86]. Perfusion neuroimaging abnormalities in professional athletes have been revealed by SPECT in the regions relevant for cognitive functions [87]. However, current data provides only partial comparability among results of structural MRI, diffusion MRI, functional MRI and MR spectroscopy.

Nevertheless, the notion of CTE as a separate disease is disputed by some authors [88]. Contrary to the expectations, longitudinal follow-up studies disclose that retired professional American football players in fact have a lower standard mortality rates and lower risk of suicide than general population [88]. Survey studies reveal mental problems only in a minority of retired American football players, with some of confounding factors being chronic pain and subsequent painkiller or alcohol abuse [12, 74]. Despite acknowledging that repetitive TBI leads to protein deposits in the brain,

pathological findings of p-tau deposits poorly correlate with clinical neuropsychological manifestations, frequently being a consequence of normal aging and not predictor of neurocognitive disease [88]. TBI is seen as aggravating the risk for earlier clinical expression of an underlying neurodegenerative disease (like AD) due to diminished neurocognitive reserve. TBI is in itself a known risk for other neurodegenerative diseases (such as AD, Lewy Body dementia) [89–91]. The exact mechanism linking TBI and dementia is not known.

Conclusion

TBI is not a single event but a chronic progressive disease which embodies long-term physical, cognitive, behavioral, emotional and possibly neuroendocrine ramifications. Some of TBIs sequelae are difficulties in daily functioning, social and occupational reintegration, family and partner relationships. TBI is a preventable and under-appreciated risk factor for several chronic neurological disabilities. Focus of post-TBI rehabilitation and intervention needs to include physical, behavioral, cognitive, emotional, personal and environmental aspects. An International Initiative for Traumatic Brain Injury Research (InTBIR) is committed to framing and promoting policies to minimize the risk of TBI and optimize the extent of recovery from TBI. Analysis of serum biomarkers (S-100β protein and others) could facilitate evaluation of TBI severity and determination of individual long term prognosis. Large well controlled studies are necessary to properly appreciate the potential prognostic role of genetic variants, blood and CSF biomarkers and early MRI scans in adult and pediatric patients with TBI.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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