6 Pathophysiology of Severe Traumatic Brain Injury

Niklas Marklund and Olli Tenovuo

Recommendations

Level I

There are no Level I recommendations for this topic.

Level II

There are no current Level II recommendations for this topic.

Level III

There are numerous observational and mechanistic studies evaluating the pathophysiology of TBI, where available data shows that a) TBI is a disease process rather than a single incident, b) there is a vast heterogeneity of TBI at both clinical and molecular levels, and c) improvement of TBI care needs to better address inter-individual differences (including age, gender, genetic/epigenetic/metabolic factors, co-morbidities) by developing targeted personalized medicine therapies.

6.1 Summary

TBI should be regarded as a disease process initiated at time of injury, complicated and markedly exacerbated by a complex set of secondary injury factors. The vulnerability of the injured brain partly explains the progressive deterioration that contributes to increased cell death, white matter atrophy, and brain network dysfunction over a period ranging from hours, days, or even years post-injury (Masel and DeWitt 2010). The damage sustained at primary impact is caused by mechanical deformation of brain tissue, resulting in neuronal and glial cell death, axonal shearing, and injury to cerebral vessels with ensuing blood–brain barrier (BBB) disruption and disturbed regulation of the cerebral blood flow (CBF) (Marklund and Hillered 2011). Key pathophysiological events are summarized in Fig. 6.1. The damage caused by the initial impact cannot be treated, only prevented. At present, rapid surgical treatment and modern neurocritical care may be lifesaving and attenuate the TBI-induced secondary injuries. However, no pharmacological treatments with proven clinical benefit are available for severe TBI, although increased understanding of the secondary injury and late

N. Marklund (✉)
Department of Clinical Sciences Lund, Neurosurgery, Lund University, Skåne University Hospital, Lund, Sweden
e-mail: niklas.marklund@med.lu.se

O. Tenovuo
Turku Brain Injury Centre, Turku University Hospital, Turku, Finland

Department of Clinical Medicine, University of Turku, Turku, Finland

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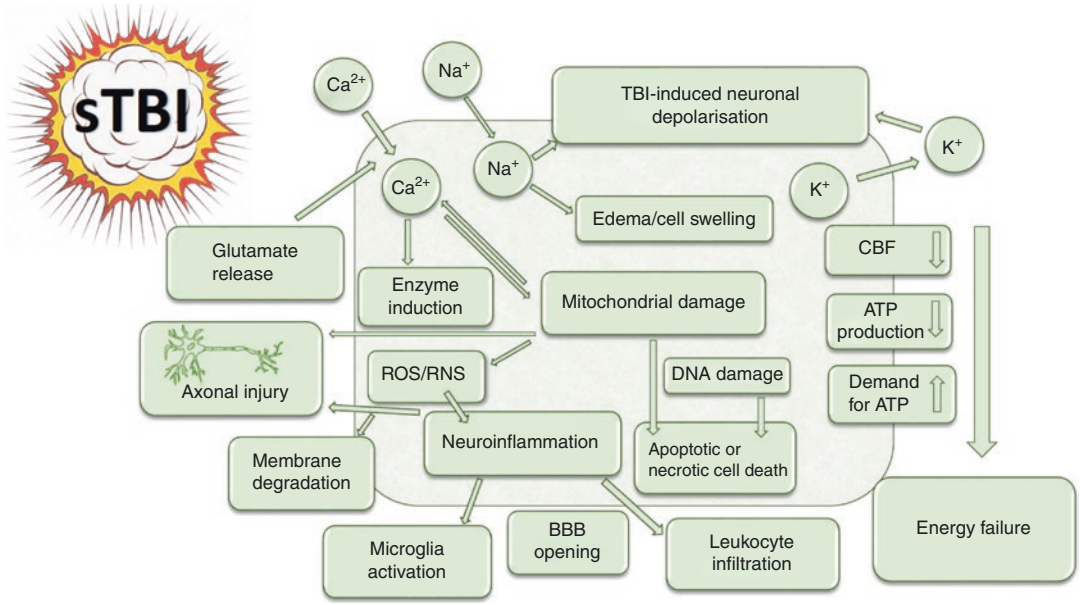

Fig. 6.1 Schematic overview of the pathophysiology of TBI. *ROS* reactive oxygen species, *RNS* reactive nitrogen species, *Ca* calcium, *Na* Sodium, *K* potassium, *CBF* cerebral blood flow, *BBB* blood–brain barrier, *ATP* adenosine triphosphate, *sTBI* severe TBI

processes raise hope for the development of novel treatments targeting both the short- and long-term factors contributing to the progressive injury. Such therapies need to target the vast heterogeneity of TBI and consider patient-specific factors, moving towards more individualized therapies (Saatman et al. 2008). Plausibly, such approaches are needed to further decrease morbidity and mortality, which remain high without marked improvements during the last decades (Stein et al. 2010).

Some of the secondary injury processes may be monitored clinically, although the detailed molecular events worsening the injury are incompletely known. Examples of the systemic factors monitored clinically in neurocritical care are covered elsewhere in this volume and include hypotension, hypoxia, hyperthermia, infectious complications, electrolyte disturbances, and hypo/hyperglycemia. Intracranial factors detected clinically using neurocritical care monitoring, clinical evaluation, and/or neuroimaging include enlargement of TBI-induced hemorrhages, cerebral edema, raised ICP/decreased CPP, seizures, and CBF impairments leading to ischemia (Kinoshita 2016). Furthermore, neuroinflammatory and neurodegenerative cascades initiated early may be prolonged and continue for years following TBI (Johnson et al. 2012, 2013a; Smith et al. 2013a; Ding et al. 2008). In the following paragraphs, the pathophysiology of severe TBI from a clinical and molecular perspective is outlined.

6.2 Pathophysiology of Severe TBI: Clinical Perspectives

6.2.1 Primary and Secondary Injuries

TBI can be classified in several ways. One of the clinically most important is the classification into primary and secondary injuries. Primary injuries include those pathophysiological events and brain lesions, which are caused by the primary trauma energy affecting the brain. These energies may be caused by a direct impact (such as when

the head hits the ground in a fall), acceleration/deceleration, or from a penetrating object. Blast-induced TBIs belong to primary injuries and comprise complex multiple mechanisms, but are rare outside war zones. Different types of primary injury mechanisms are not mutually exclusive, and it is very common that both direct impact and deceleration occur in the same incident.

Primary injuries may be either extra-parenchymal or intra-parenchymal (Table 6.1). Extra-parenchymal injuries include epidural hematomas (EDHs), subdural hematomas (SDHs), and traumatic subarachnoid hemorrhages (tSAH). Intra-parenchymal lesions are traumatic intracerebral hemorrhages, contusions, or traumatic axonal injuries. Traumatic axonal injury is usually widespread and diffuse, known clinically as diffuse axonal injury (DAI). Regularly, many of these may co-occur in the same injury, e.g. a combination of SDH, tSAH, contusions, and axonal injury is common in cases of severe TBI. The presence of a certain type of primary injury is not directly linked to TBI severity, and all types may be seen in both mild and severe cases.

Secondary injuries are various pathophysiological events that are either triggered by the primary injury or consequences of other injuries or complications, with a detrimental effect on the injured brain. Traditionally, secondary injuries have been classified into systemic and intracranial. Systemic secondary injuries include events that may exacerbate the consequences of the primary injury, often by impairing oxygen supply or cellular homeostasis. The most important and common systemic secondary injuries are hypotension and hypoxia. Intracranial secondary injuries are often consequences of the primary brain injury but not unrelated to systemic secondary injuries. Among the most important and common intracranial secondary injuries are increased intracranial pressure, brain edema, and cerebral ischemia. Table 6.2 lists the most important systemic and intracranial secondary injuries, most of which have been discussed in detail elsewhere in this book.

The devastating consequences of the secondary injuries may be exemplified by the axonal injury process. Primary axonal injury from shearing forces may occur from the initial, primary impact although it is a rare event in TBI survivors. Instead, worsening axonal injury is a slow pathological process reaching full extent weeks or months after the trauma event (Ljungqvist et al. 2017), if ever in some cases (Cole et al. 2015), as discussed later in this chapter. Similarly, brain contusions (Figs. 6.2

Table 6.1 Classification of primary brain injuries

Extra-parenchymal	Intra-parenchymal
Epidural hematoma	Contusions
Subdural hematoma	Intracerebral hematoma
Traumatic subarachnoid bleeding	Diffuse axonal injury
	Diffuse vascular injury

Table 6.2 The most important systemic and intracranial secondary injuries

Systemic	Intracranial
Hypoxia	Increased ICP
Hypotension	Brain edema
Hypo-/hyperglycemia	Convulsions/seizures
Hypertermia	Brain ischemia (focal or global)
Electrolyte imbalance	Delayed intracranial bleedings
Coagulation disturbance	
Infections	

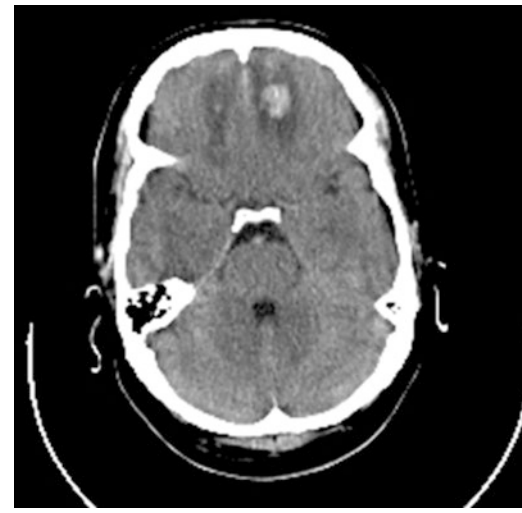

Fig. 6.2 A typical bilateral frontal contusion after hitting the occiput on the ground

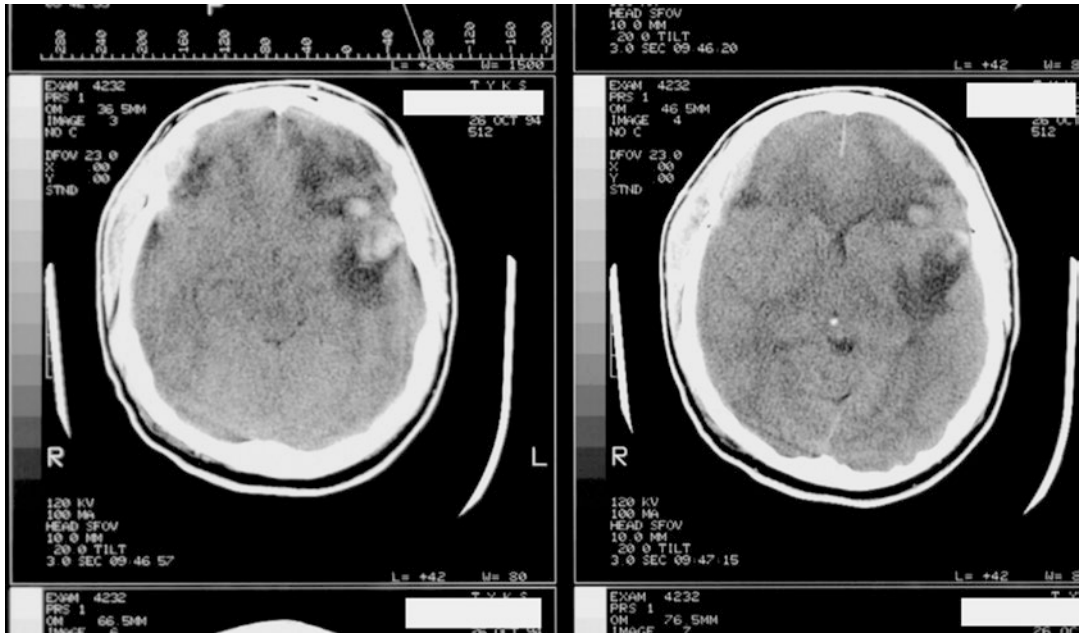

Fig. 6.3 Edema rings surrounding hemorrhagic contusions

and 6.3) may progress markedly within the first post-injury days leading to clinical deterioration. Thus, TBI is a highly dynamic disease where both rapid deterioration and a gradual, progressive decline can be observed.

6.2.2 Epidural Hematomas (EDH)

Epidural hematoma (EDH) is, according to its name, located between the skull and dura. It usually originates from a rupture of a meningeal artery, caused by a skull fracture. The middle meningeal artery injury is the most common source of the bleeding. EDH may be caused also from a venous injury, most often from a ruptured sinus in the posterior fossa, or from venous channels in the skull bone. In both cases, the amount of bleeding is often significant; hence, these usually require rapid neurosurgery.

EDH is typically the cause of the classical 'talk and die' or 'walk and die' course, when after a head trauma there is a lucid interval and the patient is in good clinical condition. The patient may not have lost consciousness at all, and the skull fracture easily escapes clinical examination if it is not depressed. As the blood collects between the skull and dura, it may rapidly lead to a deteriorating clinical situation, manifesting itself as lowering consciousness, hemiparesis, and clinical signs of brain herniation. EDH is often the reason for deaths in jail and is a main reason why patients with head trauma need frequent observation and monitoring of vital signs in the emergency department (ED). Once treated in time, the prognosis of EDH is very good if not accompanied by intracerebral lesions. Small EDHs may not require neurosurgery but need careful observation until the risk for progression is over.

EDH is more frequent in young people, because with age the dura adheres more tightly to the skull, leaving no room for an EDH. EDH is usually easy to separate from SDH on CT-imaging, by its lens-like structure, and frequent association with a skull fracture at the site of hematoma. However, a skull fracture is not a prerequisite for an EDH. In addition, EDHs do not cross epidural compartments, which are defined by the skull sutures, whereas SDHs often cover the whole hemisphere.

6.2.3 Subdural Hematomas (SDH)

Acute SDH has the worst prognosis and highest mortality of traumatic intracranial lesions (Ryan et al. 2012). SDH is usually of venous origin and located according to its name between the dura and the brain. SDH may also be caused by an arterial bleeding, but rupture of the bridging veins on brain surface is the typical cause of SDH.

SDH has much worse prognosis than EDH for many reasons, even if treated in time. First, contusions and DAI frequently accompany it. Second, SDH has a higher risk of rebleeding. Third, SDH frequently causes ischemia and metabolic disturbance in the underlying brain tissue. Fourth, brain edema frequently develops after SDH, causing elevated ICP and brain ischemia. As in the case with EDHs, small SDHs may be observed without neurosurgery, and they may spontaneously resolve within a few days or more. On the other hand, it is also common that an acute SDH leads to subacute and chronic forms of SDH, where the subdural blood has partly or wholly turned into subdural fluid collection.

The neurological symptoms from SDH are usually caused because of its influence on the underlying brain tissue, either from pure compression or ischemia and metabolic dysfunction. Because of its tendency to cause ischemia, SDH may also mimic stroke or transient ischemic attacks. Compressive effects are often easily visible on brain CT, but the neurological symptoms do not always correlate with the degree of compression because of these other potential mechanisms. If sufficiently large, the compressive effect and edema may lead to brain herniation.

SDH is usually fairly easy to recognize in brain imaging, especially when presenting as a large subdural collection of blood covering most of the hemispheric surface. SDHs may also be quite small, when distinction from an EDH is not always easy. Small SDHs located on the inferior surface of the brain may escape detection by CT imaging and be better visible on MR imaging.

6.2.4 Traumatic Subarachnoid Hemorrhage (tSAH)

Similar to other intracranial bleedings, tSAH may appear as the sole injury, or be accompanied with other types of injuries. It is usually easily separable from spontaneous aneurysmal SAH because of different localization of the blood and presentation after a trauma, as well as from SAH caused by an arteriovenous malformation. However, in some cases, this differential diagnosis is not straightforward, and it may be difficult to tell if the SAH caused the fall/injury or if the fall/injury caused a tSAH. If clinical doubt of the origin of SAH exists, imaging of brain vasculature is needed.

The severity of tSAH is very variable, ranging from small amount of blood in one cortical sulcus to large amounts of blood in the subarachnoid space, including the ventricles. If not confounded by other concomitant lesions, the amount of blood correlates strongly with the severity of clinical symptoms. Similarly as in non-traumatic SAH, subarachnoid blood disposes to vasospasms in cerebral arteries and to impaired CSF flow and hydrocephalus.

In many studies, the presence of tSAH has been a poor prognostic sign and is included in some of the CT scores with predictive value in TBI (Thelin et al. 2017). Yet, there are studies with opposite results (Nassiri et al. 2017), showing nicely the complexity of TBIs, where no single variable is able to give reliable prognostic predictions. In case of tSAH, the amount of blood, other concomitant intracranial lesions, and level of consciousness together largely determine the prognosis and not the lack/presence of tSAH itself. Indeed, small amount of tSAH without other signs of severe TBI usually has a fairly benign course (Thelin et al. 2017; Nassiri et al. 2017).

6.2.5 Contusions and Traumatic Intracerebral Bleedings

Contusion is the most common type of intracranial visible traumatic lesions. It is a typical impact lesion, although it may be caused also from pure

acceleration/deceleration, when the moving brain bruises either against the bony ridges of the skull base or inner skull surface. The vast majority of contusions are located either frontally or temporally and often bilaterally. These predilection sites are caused either by the aforementioned skull base anatomy, with bony ridges causing bruises in the overlaying frontal and/or temporal lobes in a sudden movement, or by a contra-coup injury where the side opposite to the skull impact shows the greatest brain movement against the skull. This coup/contra-coup mechanism is typical for contusions, where there may be a small contusion at the site of impact and a larger contusion on the opposite side of the brain (Fig. 6.2). In a typical ground-level fall, the posterior part of the head strikes the ground, resulting in bilateral contusions in the frontal lobes and often to a lesser extent bilaterally in the temporal lobes. Consequently, injuries of several brain lobes simultaneously are fairly common. When a person falls frontwards, usually the outstretched arms absorb most of the impact energy; hence, occipital contusions are less common. The tentorium also protects the occipital parts of the brain from contusions.

Although many contusions are visible on admission, they may also develop with delay, often becoming visible not before the second or third day from the injury. Often neurological deterioration is caused by delayed contusion progression with surrounding edema. Some of the contusions are resolving while others are expanding, with expanding ones often surrounded with a "ring" of edema and ischemia (Newcombe et al. 2013) (Fig. 6.3), resembling the classical penumbra surrounding a brain infarction or hemorrhage. Most contusions contain a hemorrhagic core and surrounding edema, with variable relationships. The terms "intracerebral traumatic hemorrhage" and "traumatic intracranial bleeding" are often used interchangeably with contusion, especially if bleeding predominates instead of local edema. Most contusions do not require surgical measures, but large superficial bleedings may require evacuation if they cause marked compression, elevated ICP, and neurological deterioration.

6.2.6 Diffuse Axonal Injury (DAI)

In the original report by Strich in 1956, widespread axonal injury was observed at autopsy 5–15 months following severe TBI. Extensive experimental and clinical results later characterized the clinical entity of DAI (Adams et al. 1982) and showed that axons and other components of the white matter were vulnerable to rotational acceleration–deceleration forces causing shear injuries. It was suggested that axonal injury was the mechanism explaining unconsciousness and prolonged coma post-TBI in the absence of focal injuries (Gennarelli et al. 1982). At autopsy, DAI was found to be characterized by β-amyloid precursor protein (βAPP) accumulations observed as either a classical axonal bulb, caused by a single large axonal swelling, or axonal varicosities with several localized swellings in a single axon (Johnson et al. 2013b). The βAPP accumulation is caused by impaired axonal transport by injury and is described in more detail in the following paragraphs.

Diffuse injuries can be classified using the Marshall CT classification, or other CT classification scores. None of these are specific for DAI. The commonly used classification proposed by Adams in 1989 is based on histopathology obtained at autopsy (Adams et al. 1989), where Grade 1 is axonal injury in the cerebral hemispheres, in particular the grey–white interface, Grade 2 axonal injury in the corpus callosum, and Grade 3 axonal injury in the brainstem. Increasing use of MRI enabled adoption of this grading scale to modern neuroimaging. In patients with severe TBI, MRI commonly reveals Grade 3 DAI, although it must be noted that also high-resolution MRI is unable to depict the full extent of axonal injury (Abu Hamdeh et al. 2017; Skandsen et al. 2010). Several recent studies have attempted to improve the prognostic use of the Adams classification by using a detailed evaluation of brain stem pathology post-TBI (Moe et al. 2018). It should be emphasized that e.g. microhemorrhages observed on CT and/or MRI is not diagnostic of DAI—it merely suggests the presence of axonal injury. Furthermore, the link between vascular injury and DAI cannot be con-

firmed on regular MRI imaging. It is now established that axonal injury is not only observed in patients with a severely depressed level of consciousness, but isolated DAI in the absence of any focal mass lesions is yet a rather infrequent finding acutely in patients with severe TBI (Skandsen et al. 2010). Instead, in up to 50% of those with focal lesions, widespread axonal pathology is also present at autopsy, and some degree of axonal injury is plausibly present in a majority of severe TBI patients (Tsitsopoulos et al. 2017).

Axonal injury commonly has a profoundly negative impact on outcome (Adams et al. 2011; Kampfl et al. 1998; Graham et al. 2005). In severe TBI, patients with "pure" DAI presenting with deep unconsciousness have a poor prognosis reflected by the extent of brain stem and/or thalamic injury. Axonal injury also induces brain network disconnections with consequences such as impairment of cognition, executive functions and attention, visualized by newer MRI methodologies such as resting state MRI and diffusion tensor imaging studies. Disruptions in important white matter tracts such as the thalamo-frontal network, corpus callosum, limbic fibers, and interconnecting pathways related to the hippocampus and the diencephalon have been revealed and are linked to cognitive deficits (Kinnunen et al. 2011; Hayes et al. 2016; Fagerholm et al. 2015).

6.3 Pathophysiology of Severe TBI: Molecular Perspectives

6.3.1 Excitotoxicity, Mitochondrial Disturbance, and Cell Death

A pivotal initiating event in TBI is the massive release of the excitatory neurotransmitter glutamate, which may act on different types of glutamate receptors. These receptors may be divided into ionotropic (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA/kainate) and *N*-methyl-D-aspartate (NMDA)) and metabotropic (mGluR1-5) receptor subtypes. In TBI, increased extracellular levels of glutamate lead to excitotoxicity due to excess activation of these receptors and the ensuing cascades that lead to detrimental intracellular effects. When high concentrations of glutamate in the synaptic cleft act on post-synaptic NMDA receptors, cation channels for calcium and sodium are opened in an uncontrolled fashion. This leads to the failure of Na+/K+ ATPase ion pump and excessive intracellular calcium levels. Furthermore, the increased intracellular calcium, which is another crucial pathophysiological event in TBI, leads to mitochondrial swelling. This, in turn, has numerous negative consequences for cell function, including impaired generation of ATP, which would be needed to restore membrane pump dysfunction. The depletion of high-energy phosphates (ATP) may be a rapid event and is associated with the increase of lactic acid and local acidosis (See Fig. 6.1).

Additionally, impaired mitochondrial function leads to increased generation of reactive oxygen species, impaired radical scavenging and release of cell death promoting molecules such as B-cell lymphoma 2 (BCl-2), apoptosis-inducing factor (AIF), and cytochrome-C. Furthermore, elevated levels of peroxynitrite contribute to the oxidation of cellular components in a process named lipid peroxidation, resulting in cell membrane dysfunction and impairment of cell function. The increased calcium levels also lead to increased activation of enzymes with destructive properties (lipases, proteases, nucleases) including caspases and calpains, dysfunction of the Golgi apparatus, and disaggregation of polyribosomes leading to impairment or dysfunction of protein synthesis.

TBI may also disrupt the delicate balance between neurons, astroglia, and the cerebral vasculature, further making the neurons vulnerable. It must be stated that although neurons have received most attention in TBI, other cell types such as glial and endothelial cells may be highly vulnerable to TBI as well. The key role of glutamate has been repeatedly ascertained, and blockade of glutamate receptors protects neurons from excitotoxicity and attenuates experimental neuronal damage in vivo. To date, attenuation of excitotoxicity has not translated into clinical treatment options, probably due to the difficulty of

achieving sufficiently high concentrations of a pharmacological compound at the immediate post-injury time point (Cheng et al. 2012; Lamade et al. 2019).

Neurons are highly complex, are not replaced following injury to a significant degree during adulthood, and may live over 100 years. A constant protection against endogenous and exogenous toxins, replacement and repair of intracellular constituents, and a continuous production of energy is needed. For cellular function, an intact cell structure and maintenance of intra–extracellular osmotic and ionic gradients is crucial. The ability to maintain membrane integrity—cellular compartmentalization—is of paramount importance and when disrupted by the previously mentioned cascades, cell death ensues. Although cell death may be considered a continuum across a spectrum of cell death mechanisms, some key mechanisms may be identified.

- **Necrosis** is considered an uncontrolled, passive, and non-programmed form of cell death, without the intricate regulatory mechanisms as observed in apoptosis. It induces inflammation of surrounding tissues due to release of intracellular contents. It is also characterized by variable morphology, loss of cell membrane integrity, and lysosomal involvement, leading to autophagic and nonlysosomal disintegration.
- **Apoptosis** is a "programmed" and active form of cell death with complex regulatory mechanisms, which require energy. In the cell nucleus, chromatin condensation and nuclear fragmentation are observed. Membranes and organelles including mitochondria are preserved during early apoptotic cell death, including the formation of apoptotic bodies densely packed with cellular organelles and nuclear fragments. These cellular constituents are phagocytized by surrounding cells, and compared to necrosis, apoptosis is "cleaner" and does not induce an inflammatory response. Apoptosis is also observed during normal development.
- **Autophagocytosis** is mainly a morphologic definition and is considered a type of cell death associated with autophagosomes and autolysosomes. There is some controversy whether this is a specific mechanism of cell death.

Under normal conditions, proteolysis of regulatory, oxidized, and misfolded proteins, as well as aggregated proteins and even organelles takes place in the proteasome. Misfolded proteins may avoid detection by the ubiquitine system, and thus escape degradation in the proteasome system. This may allow certain proteins (tau, beta-amyloid, α-synuclein, etc.) to aggregate and accumulate in the injured brain, ultimately leading to cell dysfunction and/or cell death.

Thus, a mix of cell death patterns is anticipated in TBI. Importantly, severe TBI results in a progressive atrophy of the injured brain—to the same extent to that observed in Alzheimer's disease (Cole et al. 2015). Both neuronal cell death and, most importantly, white matter atrophy contribute to the ongoing loss of brain tissue. Importantly, oligodendrocyte death has been observed in severe TBI (Flygt et al. 2016), which may contribute to the observed white matter pathology.

6.3.2 Alterations of Cerebral Blood Flow (CBF)

The delivery of sufficient blood flow is imperative after severe TBI. Under normal conditions, the brain receives about 15% of the total blood volume, uses 20% of all oxygen, and consumes 25% of all glucose, despite constituting only ~2% of total body weight. In uninjured conditions, the brain receives a CBF of 50–54 mL/100 g brain tissue/min. Critical level is considered 18–20 mL/100 g brain tissue/min, and imminent cell death occurs at a CBF <10 mL/100 g brain tissue/min. Physiologically, the energy need at rest is, to a vast majority, fully met by aerobic oxidative phosphorylation.

After TBI, the energy requirement of the brain increases tremendously for the reasons described in the previous paragraphs. Furthermore, a CBF/energy metabolism mismatch is common

(Fig. 6.1). Although the CBF levels following TBI are markedly heterogeneous and may depend on a variety of individual factors, some characteristic CBF changes may be identified. First, in severe TBI patients who have died from their injury, 90% show widespread ischemic changes at autopsy (Graham et al. 1989). However, although there is a clear reduction of CBF during the first 12 post-injury hours in about 1/3 of patients, PET studies indicate that the metabolic needs are usually met and that frank ischemia has not developed (Kawai et al. 2008; Rostami et al. 2014). During the first few days, a reduced CBF down to about 50% of normal values may be observed. Thereafter for up to 4–5 days, either a normal or increased ("luxury perfusion") CBF emerges, again followed by a second phase of reduced CBF lasting up to 2 weeks post-injury (Rostami et al. 2014). In severe TBI, the tight coupling between CBF and neuronal metabolism is typically lost. Impaired energy metabolism in TBI is not only related to CBF, but it is also related to the increased energy requirements of the brain and on the availability and use of energy substrates. Both PET and microdialysis data suggest that a metabolic depression due to mitochondrial dysfunction is common. Furthermore, early hyperglycolysis, defined as increased cerebral glucose utilization relative to cerebral energy demand, is a common feature of TBI (Glenn et al. 2003). Finally, in severe TBI frank ischemia may occur, and if so it is strongly correlated with clinical outcome, as observed in fatal TBI cases. Thus, in severe TBI cases, ischemia should be avoided at all costs, although it may be less common than previously thought.

6.4 Cerebral Edema Post-TBI

Normal ICP is commonly stated to be in the range of 7–15 mmHg. However, due to the invasive methods used to measure ICP, the assessment of a completely normal ICP has been difficult. Recently, using implanted ICP sensors following unruptured aneurysm surgery or following removal of small brain tumors, the normal ICP was estimated to be ~0.5 ± 4.0 mmHg in the supine position (Andresen and Juhler 2014). Following severe TBI, there is an inevitable increase in ICP due to e.g. hemorrhages and the accumulation of cerebral edema. The accumulation of edema may lead to increased mass effect, increased ICP, and potentially herniation. When tissue pressure increases due to swelling, there may be a capillary lumen collapse leading to cerebral ischemia, thus exacerbating the edema. In fact, cerebral edema and brain swelling after traumatic brain injury were estimated to account for up to 50% of patient mortality (Donkin and Vink 2010).

Cerebral edema can be defined as a pathological increase in the water mass contained by the brain interstitial space. The current concept of edema formation post-TBI includes a sequence of events from an initial cytotoxic edema that is rapidly followed by ionic edema and then vasogenic edema, elegantly reviewed in Stokum et al. (2016).

Cytotoxic edema occurs in the immediate post-injury minutes after TBI and is caused by influx of mainly Na+, Cl− and water from the interstitial spaces. It occurs in all cell types in the brain, although predominately in astrocytes. An important difference to the transvascular types of edema (ionic and vasogenic edema) is that cytotoxic edema does not generate tissue swelling, since it merely rearranges water in the brain. Ionic edema arises following the cytotoxic edema, occurs extracellularly, and is characterized by an intact blood–brain barrier (BBB). It is caused by the Na+ gradient generated by cytotoxic edema and is the result of extravasation of Na+ and water, with Na+ accumulating in brain parenchyma. The vasogenic edema also arises extracellularly hours after the injury and in contrast to ionic edema it includes extravasation of plasma proteins and breakdown of the BBB, allowing IgG and albumin to enter the brain interstitial space, although not erythrocytes. Surrounding TBI-induced hematomas, a perihematomal edema arises triggered by the marked toxicity of blood to brain tissue. The hematoma, and its degradation products, leads to the formation of ionic edema, vasogenic edema, and delayed vasogenic edema. Thrombin, one of the key components in a cerebral hemorrhage, is a

major contributor to the formation of perihematomal vasogenic edema by inducing an inflammatory response with the release of cytokines and infiltration of leucocytes from the circulation. The delayed vasogenic edema is mainly formed in response to hemoglobin degradation products such as methemoglobin, its heme moiety, and free iron which reaches peak tissue levels in ~3 days post-injury. Free iron is then known to lead to ROS production and BBB breakdown. BBB breakdown, known to persist up to a year or more in a significant proportion of TBI survivors (Hay et al. 2015), is another key component of edema formation in TBI. Numerous factors contribute to the maintenance of an intact BBB such as the interaction of the endothelium with e.g. neurons and glial cells that constitute the neurovascular unit (Nag et al. 2011). The BBB is crucial for maintaining cerebral homeostasis and TBI matrix metalloproteinases, as well as angiogenic factors and growth factors may be future treatment targets post-injury. Cerebral edema is a crucial injury mechanism in TBI that can partly (and briefly) be attenuated by hyperosmolar solutions such as hypertonic saline and mannitol, although much more research is needed to better refine pharmacological treatment options.

6.5 Inflammation and Immunity

Traditionally, TBI has been considered as an acute mechanical injury, and only recently, the possible major role of immunological aspects has been recognized. The disruptive energy forces of TBI predispose the brain for immunological cascades at least by two different mechanisms: cell death and necrosis liberating pro-inflammatory substances from cells; and disruption of the BBB allowing circulating immune cells to enter the brain. In addition, some aspects of the immune reactions triggered by a TBI can be classified as beneficial, aiming at limiting the injury and destroying harmful constituents released by the injury, whereas others are detrimental, considered to exaggerate and prolong immune responses resulting in chronic inflammation and progressive damage. Furthermore, the immunological responses and cascades can be classified as local, affecting the brain and injured brain regions; or systemic, affecting the whole body.

The immunological reactions triggered by a TBI involve a variety of immunological cells and mediators: neutrophils, macrophages, microglia, T-cells, and a large number of cytokines and other immunological mediators (McKee and Lukens 2016). The rapid immunological events occurring after TBI are purposeful protective reactions, aiming at neutralizing harmful mediators, cell constituents, and other potentially toxic substances. This complex acute immunological reaction subsides, and slower, reactive inflammatory processes will be activated. These aim at stabilizing the pathophysiological cascades, and initiating scarring and other healing measures. It appears that these physiological mechanisms may be considered a double-edged sword, turning into prolonged and exaggerated inflammatory reaction escaping proper control, and leading to chronic neuroinflammation and secondary brain damage (Simon et al. 2017).

Although still quite poorly known, the immune system may have a major role as a predictive factor in patients with TBI. Elevated cytokine levels are strongly associated with poor outcome (Di Battista et al. 2016). This is logical: the more severe TBI, the stronger is the immunological response. More interesting is the role of the immune and inflammatory systems in long-term processes and outcome. For reasons still poorly known, about 20% of patients with TBI do not show expected recovery after the acute phase, but rather show a slow constant and chronic decline (Wilson et al. 2017). Although the explanations for these poor outcomes are apparently multifactorial, there is increasing evidence from both experimental and human studies that chronic neuroinflammation may be a cause of this unfavorable outcome (Faden and Loane 2015). This has also raised hope that this course could be inhibited or reversed by anti-inflammatory therapies and that the time window for these interventions may be very long. Thus far, clinically useful interventions have not been found, but research in this field is active. Why only some patients

with TBI have this adverse clinical course is not known, but it seems likely that genetic properties might play a role.

Not only does the immune system affect the injured brain, since experimental studies suggest that a severe TBI has a permanent effect on the immune system, leading to accelerated immune aging and chronic deficits in the immune system (Ritzel et al. 2018). This might be one explanation for TBI as chronic disease, which not only has an additive effect with aging phenomena but also is disease-causative (Masel and DeWitt 2010).

6.5.1 Pathophysiology of Axonal Injury

The principal mechanism resulting in axonal injury is rotational acceleration–deceleration forces resulting in deformation of the brain tissue, surpassing the resilience to mechanical stretch of the uninjured brain. Due to the variable densities of gray and white matter, rotational forces result in tension at the gray/white matter interface (Andriessen et al. 2010), and a rapid stretch of the axon will result in injury to the axonal membrane, then leading to injury of the axonal cytoskeleton. Primary axotomy has been observed in very severe TBI in patients dying at or shortly after the injury, but it seems to be rare in those who survive longer times after a TBI. Instead, a cascade of events will trigger axonal pathology leading to delayed axotomy (Smith et al. 2013b; Hill et al. 2016). The TBI-induced axonal stretch initiates opening of sodium channels, with ensuing calcium influx. The rapid increase of intracellular calcium then leads to the activation of calpains and caspases, which then causes disruption of microtubuli and neurofilaments. The injury to the cytoskeleton leads to impaired axonal transport, both antero- and retrogradely. This disturbs neuronal functions and leads to intra-axonal accumulation of numerous proteins and axonal swelling, which in turn may cause delayed axonal transection. In severe axonal injury, rapid opening of the axolemma with loss of control of membrane permeability—axonal mechanoporation—leads to further exacerbation of calcium influx, distal axonal fragmentation and axonal disconnection. Furthermore, the rapid calcium influx results in local mitochondrial damage with subsequent increase in the release of reactive oxygen species (ROS) and an impaired energy metabolism. In the event of axonal transection, the distal axonal segment will undergo a process of disintegration—the Wallerian degeneration.

These events are initiated early post-injury and then progress over the course of days to weeks or even longer. As noted in the previous section, βAPP is the hallmark histopathological finding of axonal injury and is detected in injured and swollen axons. βAPP is the precursor of β-amyloid (Aβ) species, found aggregated in the brains of Alzheimer's disease (AD) victims. βAPP-degrading enzymes such as presenilin-1 and beta-site APP-cleaving enzyme (BACE-1) also aggregate within injured axons, leading to the accumulation of Aβ peptides (Chen et al. 2004). In addition, immunohistochemistry and PET studies have shown prolonged accumulations of Aβ years after the injury (see Chap. 86). The small, monomeric Aβ peptides may also assemble as large soluble oligomers, forming protofibrils. Plausibly, the Aβ oligomers and protofibrils may be important factors resulting in neurotoxicity following TBI (Abu Hamdeh et al. 2018). The soluble protofibrils may subsequently form the insoluble fibrils typical of Aβ plaques observed in TBI and in AD. Intriguing data show that Aβ plaques, developing over many years in AD, are deposited in the brains of about a third of TBI victims within the first post-injury days. The aggregation of Aβ seems to be linked to the genetic presence of the ε4 allele for the lipid transporter protein apolipoprotein E (APOE ε4), a well-known risk factor for both AD and worse outcome following TBI (see Chap. 86).

In AD, the hallmark histopathological finding is not only the Aβ plaque but also neurofibrillary tangles (NFTs) consisting of hyperphosphorylated tau (P-tau) protein. Tau is microtubule-associated, and its physiological activity is regulated by the degree of phosphorylation. Hyperphosphorylation may cause aggregation of

tau into NFTs, and increased tau release is associated with axonal injury and a worse clinical outcome (Magnoni et al. 2012, 2015). In long-time survivors of TBI, increased numbers of NFTs were observed at autopsy, similar to Aβ deposits (Johnson et al. 2012), suggesting a persistent pathophysiological process causing NFT aggregation that may be linked to axonal injury. Severe TBI is a known environmental risk factor for AD (see Chap. 82). The mechanisms outlined here may be contributing to the link between TBI and various neurodegenerative disorders, although the exact role of axonal injury in these processes remains to be established.

Although axonal injury has received and deserved most scientific attention, there are other components of the white matter that may contribute to the pathophysiology of TBI. Importantly, white matter degradation has been shown to persist for years following TBI, linked and associated with a persistent inflammation (Johnson et al. 2013a). Myelin injury has also been observed in both the experimental and clinical TBI setting. Recently, death of the myelin-producing oligodendrocytes (OLs) was observed in human TBI, associated with an increased number of the resident oligodendrocyte progenitor cells (OPCs). Obviously, loss of mature OLs may lead to impaired neuronal signaling and to increased axonal vulnerability. Whether the increased number of OPCs may replace the lost OLs and/or lead to remyelination of demyelinated axons remains to be established. Also, even though myelinated axons have been more extensively studied, unmyelinated axons may have a higher vulnerability to injury, which needs further studies.

Unfortunately, central nervous system (CNS) axons do not spontaneously regenerate after injury. Important contributors to the restriction of CNS plasticity are the myelin-associated inhibitors (MAI (Johnson et al. 2012), Fig. 6.4), including the molecules Nogo-A, myelin-associated glycoprotein (MAG), and oligodendrocyte-associated glycoprotein (OMgp), all sharing the NgR1 receptor. After injury, the expression of Nogo-A increases, which may lead to the activation of numerous down-stream cascades, ultimately leading to a failure of axonal regeneration. Furthermore, neuronal-intrinsic factors specific to the CNS may be additional contributing factors to the inability of CNS axon regeneration (Armstrong et al. 2016; Geoffroy and Zheng 2014).

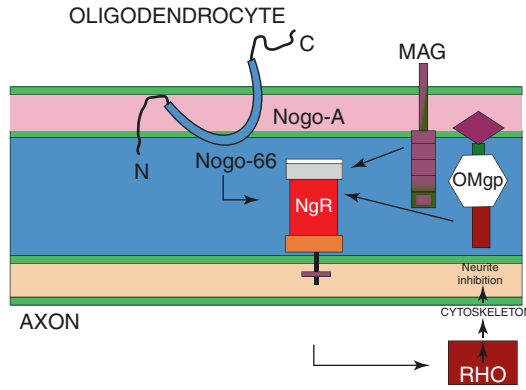

Fig. 6.4 Heavily simplified overview of the factors contributing to the absence of outgrowth possibilities following axonal injury in the adult CNS. *NgR* Nogo-66 receptor 1, *MAG* myelin-associated glycoprotein, *OMgp* oligodendrocyte-myelin glycoprotein

6.5.2 Temporal Aspects

TBI and especially severe TBI is a very dynamic injury. Both rapid recovery and sudden deterioration are common and well-known clinically. At the molecular and cellular level, all the various pathophysiological cascades have different temporal courses, both what comes to the initiation and duration of the injury process. During the first hours and days, edema formation, neutrophil activation, necrosis, excitotoxicity, and calcium influx are the prevailing events. After a few days post-injury, apoptosis and microglial activation emerge, while e.g. necrotic cell death has subsided. Later, demyelination, neuronal disconnection, neuroinflammation, and Wallerian degeneration become important, and epileptogenesis may start developing. Although all these different pathophysiological processes have their typical courses and time windows, individual differences may be marked due to several reasons, both injury- and treatment-related, as well as genetic.

One of the main reasons for lack of major progress and lack of targeted therapies for TBI has been insufficient knowledge of the pathophysiological cascades, and especially lack of tools to detect and monitor them. Targeted interventions cannot be developed, if ways to measure the presence and severity of the target pathophysiology are not available. This temporal variability and complexity are big challenges both for the clinical conventional diagnostics and for new diagnostic tools. For example, the optimal time for using different MRI sequences to detect TBI-related pathology is not known. Continuous monitoring of the gross cerebral physiology at the ICU tries partly to overcome these challenges and helps to prevent and treat some secondary injuries. However, the cellular mechanisms behind most events remain unknown, and thus the treatments are often made on a "best guess" basis. Microdialysis (see Chap. 42) may aid in solving these problems, and it helps to determine if deterioration is caused by ischemia or mitochondrial failure, guiding treatment decisions.

The active research on brain-injury biomarkers has also suffered from simplistic views, as if one sample (and one biomarker) at admission could give sufficient information. It has become evident that the complex and dynamic events of TBI have to be measured and monitored by serial samples of a panel of biomarkers, thus enabling to determine which processes are emerging and which ones are subsiding. This kind of approach is especially important in severe TBI, where multiple mechanisms may be operating at different time points.

6.6 Recovery Mechanisms and Plasticity

As discussed in more detail elsewhere in this book, the unpredictable outcome remains a major challenge for the clinicians. This is true for both short- and long-term predictions. During the acute stage, the clinical course of a severe TBI may take sudden turns, not only towards worse outcome but often also unexpectedly towards recovery. While these may often have obvious treatment-related causes, such as drug-related effects, there are also biological processes, which may manifest unpredictably.

During the acute phase, recovery mechanisms are only beginning to emerge, but fairly rapid improvement of the clinical stage may be observed due to resolving edema, cessation of cortical spreading depression or epileptiform activity, or reversal of subtle brain ischemia. During the first days and weeks, true recovery mechanism will become active (Mannino et al. 2018) and start by both limiting the injury and its consequences, as well as promoting regeneration and plasticity.

During the subacute period following severe TBI, it is clinically difficult to separate the contribution of resolving pathology from active recovery as a driver for clinical recovery. Biological mechanisms favoring recovery during this period include at least partly remyelination, immunological neutralization of toxic substances and constituents, and metabolic adjustment including increased CBF and glucose and energy metabolism. However, at least on an individual level, it is difficult or impossible to determine when these phenomena are signs of active recovery and when caused by chronic damage. All these alterations have been reported also at the chronic stage (McGuire et al. 2019) obviously reflecting the increased needs of the injured brain.

Long-term follow-up studies show that at least 50% of patients with TBI gradually improve over time, in some cases substantially. The mechanisms for recovery are intriguing in view of the lack of axonal regeneration and that lost neuronal cells are not replaced to a significant degree within the injured brain. Instead, a key mechanism for recovery is endogenous plasticity, which is in turn affected by both environmental and genetic factors. The molecular mechanisms leading to brain plasticity after TBI remain poorly understood, although sprouting of both local and long-range axonal projections, synaptic plasticity with altered neurotransmission, and re-shaping of the neuronal networks (Bose et al. 2015) may all be involved. Several neurotrophic substances and neurotransmitters have been shown or suggested to regulate and/or promote plasticity. Most

experimental studies have focused on cortical mechanisms (Wolpaw 2007; Pruitt et al. 2017; Axelson et al. 2013; Combs et al. 2016), although recent data suggest that plasticity may occur in the entire CNS, including the spinal cord, and be related to behavioral recovery (Wolpaw 2007; Sist et al. 2014; Tennant 2014). Rehabilitative efforts such as enriched environment as used in the experimental setting and/or physical activity may stimulate endogenous neuroplasticity pathways (see e.g. Petzinger et al. 2013) and factors known to reduce brain plasticity may lead to a worse long-term outcome (Yue et al. 2017) implying an important role for plasticity in the CNS. It must be noted that CNS plasticity may be both beneficial and maladaptive (Tennant 2014), where examples of maladaptive post-injury plasticity include the development of spasticity and epilepsy. Still, promotion of plasticity is likely a key future treatment option for severe TBI. As such treatments are yet to come, the only clinical options are to promote plasticity with rehabilitation and to avoid factors that may interfere with these mechanisms. There is experimental evidence that some commonly used CNS-active drugs such as phenytoin, classical antipsychotics, and benzodiazepines may be detrimental and should possibly be avoided (Goldstein 1995). The timing of these agents may be crucial in this respect, and acute use does not possibly interfere with plasticity, which is a later process. This seems to be supported by clinical experience.

6.7 Conclusion

Severe TBI is among the most complex diseases known, and the vast individuality in injury mechanisms, genetic properties, and brain health makes the treatment of severe TBI extremely challenging. Although the macroscopic injury mechanisms are fairly well known, our knowledge of the cellular and molecular mechanisms is still insufficient. Research efforts should address ways to detect and assess these mechanisms, which would then enable developing of targeted therapies for various pathophysiological cascades. Past failures in bringing promising pharmacological agents from experimental studies to clinics are mainly due to lack of tools to control the vast heterogeneity of human severe TBI.

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