PERSPECTIVE

Moderate/severe traumatic brain injury as a trigger of chronic neurodegeneration in humans

Traumatic brain injury (TBI) is the paradigmatic example of acute brain injury, defined as sudden and unexpected structural and/or functional damage to the brain. In western countries, TBI is a main cause of prolonged disability, and it is even more impactful because it very often affects young people. Contrary to past belief, the cerebral damage caused by TBI is not limited to the short temporal phase following the mechanical insult. Indeed, moderate/severe TBI can trigger several mechanisms of neuronal damage that operate for months or years after the acute injury, potentially leading to neuronal loss and brain atrophy. Very little is currently known about these processes, and their real impacts in long-term survivors of TBI are largely underestimated. In this perspective, we discuss the existing evidence that moderate/severe TBI triggers various mechanisms capable of inducing prolonged neurodegeneration in humans.

Amyloid aggregation: Aggregation of the amyloid-β (Aβ) peptide is a key factor in the pathophysiology of Alzheimer's disease, the most common cause of intellectual decline in the elderly population worldwide. Whereas epidemiological studies conducted in the past two decades have led to the postulation of a link between TBI and dementia, evidence for abnormal amyloid metabolism after moderate/severe TBI has been provided only recently. The most convincing results arise from two lines of research, based on the imaging of Aβ deposits in the brain with positron emission tomography (PET) and on the detection of Aβ levels in cerebrospinal fluid (CSF) with specific immunoassays, respectively.

In a PET study in which ^{11}C-Pittsburgh compound B (^{11}C-PiB) was used to image Aβ plaques in long-term survivors of TBI (Scott et al., 2016), ^{11}C-PiB binding was greater in patients with TBI than in controls. Interestingly, ^{11}C-PiB binding correlated with the time since TBI, and its spatial distribution differed partially from that found in patients with Alzheimer's disease. The latter observation suggests that different mechanisms lead to Aβ deposition in TBI and in Alzheimer's disease. In addition, abnormal Aβ deposits may be found decades after TBI. Another PET study, for which Vietnam War veterans with and without non-penetrating TBIs were recruited (Mohamed et al., 2018), showed increased brain uptake of the amyloid tracer [^{18}F]-AV45 in veterans who had experienced TBIs. Few patients with TBIs have been included in longitudinal PET investigations to follow changes in amyloid deposits. A report of two cases evaluated with PET scans at 1, 12, and 24 months after severe TBI showed reduced [^{18}F]-AV45 uptake in some brain areas and increased uptake in other areas at 12 and 24 months compared with the 1-month evaluation (Gatson et al., 2016).

Direct information on Aβ metabolism can be obtained by evaluation of the $A\beta_{1–42}$ peptide in CSF. Reduced $A\beta_{1–42}$ and increased total tau and phosphorylated tau CSF levels are well-established biomarkers of Alzheimer's disease. In a study conducted with patients in the chronic phase following severe TBI (Bagnato et al., 2018), we found reduced $A\beta_{1–42}$ CSF levels in 14 of 15 patients, with the magnitude of reduction ranging from 18% to 82% of the lower normal limit. In that study, the $A\beta_{1–42}$ CSF decrease was not paralleled by a total tau and phosphorylated tau increase (a single patient showed only a slightly increased phosphorylated tau level). These results suggest that Aβ and tau are affected differently in the chronic phase of severe TBI and in Alzheimer's disease.

Chronic inflammation with microglia activation: Inflammation, together with mitochondrial dysfunction and neurotransmitter-mediated neurotoxicity, is a major player in determining secondary brain injury after TBI. Although activated resident immune cells of the central nervous system, in combination with migrating immune cells from peripheral blood, operate as scavengers of dead cells and may promote some neuroregenerative processes immediately after TBI, neuroinflammation also increases brain edema, causes cell death, and contributes to the disruption of blood-brain barrier integrity. In this picture, the microglia, the main immune cells of the central nervous system, play a central role. Convincing evidence suggests that microglial activation is not limited to the acute phase of TBI, but persists for months or years after moderate/severe TBI. An immunochemical autoptic study showed the persistence of activated microglia (i.e., CR3/43- and/or CD68-immunoreactive) in most cases at a mean time of 3 months after a single TBI (Johnson et al., 2013). Among patients surviving for > 1 year, these reactive microglia were found in 28% of cases and up to 18 years after TBI. Notably, evidence of ongoing white-matter degradation was also observed in cases displaying this inflammatory response (Johnson et al., 2013).

Microglial activation can also be imaged *in vivo* with PET ligands that bind to the translocator protein expressed by the mitochondria of activated microglia. In patients studied at least 11 months after moderate/severe TBI, microglial activation was found in several cortical and subcortical regions involving the gray and white matter, but not at the primary sites of brain injury (Ramlackhansingh et al., 2011). These results suggest that a long-term inflammatory response is maintained by a mechanism that differs from those operating at the original main site of brain injury. To discern whether this prolonged microglial activation is conducive or detrimental to the recovery of brain functions is of the utmost importance for the development of appropriate neuroprotective strategies. In a recent study, minocycline was administered to reduce chronic microglial activation in survivors of moderate/severe TBI, and microglial activation and neurodegeneration were evaluated with PET, MRI, and serum biomarkers of neurodegeneration (Scott et al., 2018). It showed that the reduction of microglial activation was paralleled by increased neurodegeneration, suggesting that microglial activation has some neuroprotective affects. Since the functions of microglia in the central nervous system are very complex, activated microglia may be involved in promoting both neurodegeneration and neuroregeneration in the chronic phase of TBI. As the microglia comprise a potential target for therapeutic strategies in patients with chronic TBI, their role in governing the balance between neurodegeneration and neuroregeneration needs to be investigated further.

Atrophy of the white and gray matter: TBI leads to a loss of brain volume that involves the gray and white matter. A recent longitudinal volumetric MRI study showed that patients with moderate/severe TBI had smaller gray- and white-matter volumes in multiple brain regions at baseline, and about 2.5- and 5.7-fold greater loss of gray and white matter, respectively, at 1 year compared with healthy controls (Cole et al., 2018). Cortical contusions with gray matter damage and diffuse axonal injury are very common in TBI, and they may, at least in part, explain the loss of gray and white matter immediately after the acute phase of TBI. However, the increased rate of brain volume loss in the months following TBI implies that this type of injury triggers mechanisms leading to the sustained death of axons and cell bodies.

Axonal degeneration in chronic TBI seems to primarily affect large myelinated axons. The neurofilament light chain (NF-L), a protein of the axonal cytoskeleton involved in maintaining axonal morphology and diameter, is a well-established marker of large myelinated axon injury or degeneration. CSF NF-L levels are markedly increased for up to 19 months after severe TBI, ranging from 2.4- to 60.5-fold the upper normal limit (Bagnato et al., 2017). These values are higher than observed among patients with Alzheimer's disease, which also leads to elevated NF-L levels. Axonal degeneration after TBI seems to affect large myelinated and nonmyelinated axons differently. In contrast to NF-L, total tau is expressed mainly in nonmyelinated axons of cortical interneurons. Total tau CSF levels are normal in the chronic phase of severe TBI (Bagnato et al., 2018), suggesting that nonmyelinated axons are spared by significant processes of axonal degeneration.

In volumetric MRI studies, gray-matter atrophy has been ob-

served in cortical and subcortical regions after moderate/severe TBI (Cole et al., 2015; Drijkoningen et al., 2017). The brains of patients who have sustained TBIs appear to be "older" than expected according to their chronological ages (Cole et al., 2015). Further evidence for chronic neuronal loss in patients who have suffered severe TBIs arises from the evaluation of biomarkers of neuronal loss. After the acute phase of severe TBI, patients' serum levels of neuron-specific enolase (NSE) are similar to those of matched control subjects until 1 year post-TBI, after which they decline significantly (Bagnato et al., 2019). As NSE is released mainly by neurons, these data may reflect progressive brain atrophy with reduced baseline NSE release in the chronic phase of severe TBI. Although convincing evidence indicates that brain atrophy involving the gray and white matter occurs with chronic TBI, whether the progressive loss of gray matter is secondary to axonal degeneration, or whether different mechanisms contribute independently to white and gray matter loss, is still unclear.

Concluding remarks: Compelling evidence shows that moderate/severe TBI acts as a trigger for several neurobiological processes resembling those operating in neurodegenerative diseases. However, several main questions about the underlying pathophysiology and clinical effects remain unanswered. First, we have not identified the initial neurobiological event that activates a cascade of neurobiological mechanisms leading to the loss of white and gray matter after TBI (**Figure 1**). Aβ aggregation and microglial activation are convincing candidates for this role, but their reciprocal interaction after TBI is not well understood. Aβ is known to aggregate, inducing microglial activation, and the microglia release inflammatory mediators such as cytokines, complement components, chemokines, and free radicals that contribute to Aβ production and aggregation. To date, no data demonstrate whether these processes operate in parallel after moderate/severe TBI, or whether one is the consequence of the other.

Second, the clinical consequences of the mechanisms leading to the loss of white and gray matter are largely unknown. Moderate/severe TBI has been supposed to increase the risk of neurodegenerative diseases such as Alzheimer's disease, but only a small percentage of patients who have sustained TBIs develop Alzheimer's disease. Considering the evidence for accelerated brain atrophy after TBI (Cole et al., 2015, 2018), the loss of brain volume is unlikely to occur without clinical correlates in patients who do not develop a definite neurodegenerative disease according to the current criteria. This topic is very difficult to study, as longitudinal neuropsychological assessments are required to distinguish progressive cognitive deficits from those that are the consequences of the original TBI. Depending on individual genetic and environmental factors, the effects of long-term white- and gray-matter loss after TBI may reasonably range from the absence of clinical signs to neurogenerative disease (**Figure 1**).

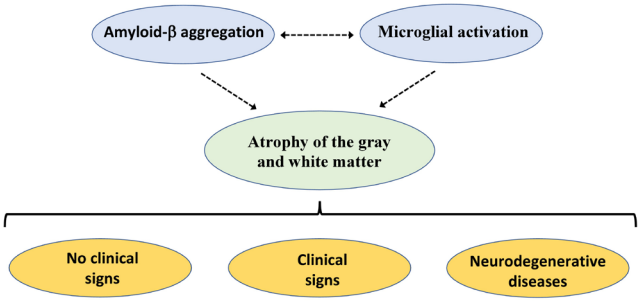

Figure 1 Proposed mechanisms and effects triggered by severe/moderate TBI.
After the acute phase of severe/moderate TBI, amyloid-β aggregation and activated microglia are probably involved in determining brain atrophy with white and gray matter loss. The dotted lines indicate hypothetical relationships. The clinical consequences of brain atrophy caused by TBI may range from the absence of clinical signs to the development of neurodegenerative disease in a small percentage of patients. TBI: Traumatic brain injury.

In conclusion, although we currently know some of the neurobiological events operating in the chronic phase of moderate/severe TBI, several pieces must still be placed in their correct positions to compose a complete mosaic of events leading to neuronal loss and brain atrophy. Exhaustive knowledge of these mechanisms will be of the utmost importance for the development of the most appropriate neuroprotective strategies to prevent the long-term effects of moderate/severe TBI.

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