Delirium and Agitation in Traumatic Brain Injury patients: an update on pathological hypotheses and treatment options.

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Abstract

Traumatic brain injury (TBI) is a global public health epidemic. It represents the principal cause of death and disability in individuals under 35 in the United States. In the subacute phase, severe TBI patients who recover consciousness go through a state of agitation and delirium. However, there is only limited research exploring the characteristics of post-traumatic delirium (PTD) although it is likely to be more frequent than in general Intensive Care Unit (ICU) patients.

Evidence suggest the incidence of delirium in non-TBI ICU patients is up to 86%. The exact pathophysiological mechanisms underlying the development and progression of delirium in critically ill patients is still unclear. Many hypotheses have been proposed to play a role: neuroinflammation, neurotransmitter imbalance, structural and functional brain damage. TBI patients are at high risk of post-traumatic cognitive impairment, and up to two thirds of patients who survive TBI develop agitation and delirium which is associated with increased disability and long term cognitive impairment. Recommendation for the treatment of PTD in patients admitted to ICU are not clearly identified. Despite the high prevalence of PTD, the condition often goes misrecognised and attributed primarily to the injury itself. There is increasing evidence that certain drugs such as antipsychotics can reduce the incidence and severity of delirium, whereas other drugs such as dexmedetomidine and remifentanil are associated with decreased risk of developing delirium in general ICU patients. However, there is a lack of high quality studies exploring treatment strategies for PTD in the acute setting.

Keywords:

Traumatic Brain Injury
Delirium
Agitation

Background

Traumatic brain injury (TBI) may be defined as an alteration in brain function and consciousness which results in impaired cognitive and physical status caused by an external force. Its incidence is steadily increasing, and TBI is now recognized as a global public health epidemic, projected to become the world's leading cause of neurological disability across all age groups by 2020 according to the World Health Organization.

TBI can adversely affect both short-term and long-term cognitive functioning, with subsequent behavioural and emotional burden for patients and their relatives. Of note, after 1 year of TBI, 21.3% of the patients may have at least one psychiatric disorder [1].

One of the most common early cognitive dysfunction is post-traumatic agitation and delirium (PTD): a confusional state, characterized by fluctuation in mental status and in attention, presenting either as disorganised thinking or as altered level of consciousness (hyperalert/agitated/lethargic), slurred speech and acute onset motor signs (tremor, myoclonus, asterixis). PTD can occur in up to half of patients with mild to moderate TBI in the first 4 days after the trauma [2]. Currently, the evaluation of acute and chronic neuropsychiatric consequences in TBI patients follows the DSM-V classification [3]; however, previous reports based on DSM IV criteria showed that approximately 70% of TBI patients met diagnostic criteria for delirium, even during inpatients rehabilitation [4]. These diagnostic criteria include symptoms such as sleep-wake cycle disturbance, abnormal motor behaviour, liability of mood, perceptual disturbance, delusions and hallucinations (see a diagnostic tools summary in Table 2).

PTD needs to be differentiated from delirium states seen in patients admitted to intensive care unit (ICU) without anatomical brain damage, from which it differs both in terms of prevalence and pathophysiology. The incidence and duration of PTD is higher than that of delirium in non-TBI ICU patients, nonetheless the two conditions have commonalities in terms of pathological basis and pharmacological management [5-7]. As PTD is a constellation of symptoms often frequent in the early phase of recovery from TBI its underlying pathology, diagnosis, prevention and treatment strategies in this population need to be elucidated.

Working theories

TBI initiates a series of processes inducing molecular, biochemical, and cellular changes within the central nervous system (CNS) resulting in neuronal damage and cellular death. This cascade of events – often referred to as "secondary injury" – occurs over hours or days and is characterised by blood-brain barrier dysfunction, altered homeostasis and cerebral metabolic imbalance, mitochondrial dysfunction, excitotoxicity and ultimately results in CNS damage [8]. The pathophysiology of PTD is multifactorial and not completely understood. Whilst its substrate is certainly CNS damage secondary to trauma, its progression is uncertain. Three dominating pathophysiological hypotheses include neuroinflammation, neurotransmitter imbalance and structural damage with disruption of neuronal networks [9] (Figure 1 and Table 3).

Neuroinflammation

Neuroinflammation is currently one of the leading hypotheses for PTD pathophysiology. Following traumatic brain injury, activation of astrocytes and microglia results in the release of multiple cytotoxic substances including pro-inflammatory cytokines and oxidative metabolites (e.g. nitric oxide, reactive oxygen and nitrogen species) [10,11]. The basis of this hypothesis is glial activation, infiltration apoptosis death [12]. The risk of developing PTD varies significantly amongst different patient populations: patients with prior cognitive disease are likely to already have ongoing inflammatory changes, including microglial priming, predisposing them to PTD following minor clinical insults [12,13].

Neurotransmitters Imbalance

Experimental and clinical evidence suggest that derangements in cholinergic, serotoninergic and dopaminergic systems may contribute to any form of delirium including PTD. Other neurotransmitters such as epinephrine, norepinephrine, glutamate and GABA are likely to play a role but a detailed mechanistic explanation of neurotransmitter imbalance leading to PTD remains elusive. Cholinergic neurons in the hippocampus are essential for attention and memory processing and are commonly disrupted by temporal base contusions [14]. In animal models of TBI, compensatory changes in acetylcholine storage and decreased presynaptic inhibitory receptors are seen and these changes correlate with loss of learning and memory [15]. Of note, cholinergic deficiency can be present for numerous reasons in ICU patients without history of brain injuries (e.g., opioids, general anaesthetics) [16,17]. Furthermore, there is a complex cortical relationship between norepinephrine, dopamine and cholinergic pathways. Disturbances in the native balance may contribute to delirium pathophysiology [17,18]. According to the monoamine axis hypothesis, dopamine, norepinephrine and serotonin excess and their respective amino acid precursors are associated with cognitive dysfunction [19].

Anatomical Brain Damage

The primary brain injury through penetrating trauma or coup/contre-coup trauma may affect different anatomical areas of the brain [20]. Patients who recover from coma secondary to TBI invariably manifest some degree of cognitive impairment, with outcomes ranging from complete recovery to vegetative or minimally responsive state [21,22]. Most patients progressively recover from a confused state but are left with varying degrees of persistent cognitive impairment and/or behavioural changes [23]. Abnormal resting-state functional networks may underlie the pathophysiology of delirium. Disruptions in reciprocity between the posterior cingulate cortex and the dorsolateral prefrontal cortex and disruptions in interregional connectivity among the acetylcholine/dopamine-related subcortical regions appear to play a pathological role in delirium, whereas enhanced connectivity in the posteromedial default-mode network may be related to rapid improvement [24]. Also, any damage to the limbic system (hippocampus, amygdala, orbitofrontal cortex and entorhinal cortex) and frontal lobe tends to affect long-range cortico-cortical connections which support large-scale brain networks, substrate of higher cognitive

functions such as emotional integration, attention and behavioural coherence. Injuries to these areas can induce irritability, anger, disinhibition, or emotional lability [25]. Recent evidence corroborating specific anatomical vulnerability demonstrated the high incidence of acute PTD symptoms in patients with haematomas in the right para-hippocampal region and parietal lobe [26].

Prevention and Treatment

A set of recommendations by the French SOFMER group reviewed the care management of subacute neurobehavioural disorder following TBI [27] including pharmacology options for agitation after TBI [28]. Unfortunately, due to the lack of distinction between acute and rehabilitation setting treatment strategies, no specific considerations are provided regarding the management of PTD in ICU. The 2013 Pain Agitation and Delirium (PAD) Guidelines [29] provide an ICU-tailored approach which need adaptation to the special needs and physiology of TBI patients. Physical and pharmacological strategies are summarised in Table 1 and future research treatment option in Table 3.

General Measures

The literature about prevention of PTD refers mostly to rehabilitation settings [30]. These include measures to improve orientation of patients to their surrounding such as clear and succinct communication, sign-posting and consistent staffing. Emotional support through involvement of family and carers, providing an unambiguous hospital environment, improving patient involvement in treatment plan and feedback about their symptoms also contribute towards delirium prevention.

Daily Interruption of Sedation and Sedative Drugs

The evaluation and treatment of PTD among ICU patients recovering from TBI remains challenging and is affected by many potential confounders, including the need of sedation to facilitate care in the acute phase and the actual progression of the underlying neurological injury. Despite increasing knowledge of the harmful effects of unnecessarily deep sedation in the general ICU population [29] and new approaches to decrease over-sedation [31], many ICU patients still spend considerable time on deep sedation. Sedation for neurocritical care patients is also indicated as a neuroprotective measure, with the impossibility of undertaking an accurate neurological assessment somewhat mitigated by the availability of multimodality neuromonitoring [32]. The risks, benefits, and role of sedation interruption or wake-up tests for brain-injured patients remain uncertain [33]. On one hand, propofol interruption among patients with TBI may result in ICP increases [34,35]; on the other hand, given their half-life a complete wash-out of sedative drugs may not always be possible within a short time-window. In mechanically ventilated adult ICU patients at risk of developing delirium, dexmedetomidine infusion was associated with a lower prevalence of delirium compared to benzodiazepine and opioids infusion [29]. A recent randomized controlled trial (RCT) showed no cerebral physiological differences between propofol and

dexmedetomidine sedation in a cohort of neurocritical care patients [36], whereas the latter seemed to reduce cerebral blood flow in patients without brain injury [37].

Beta-Blockers

The efficacy of beta-blockers in agitation after TBI in the ICU setting is based on a single controlled study vs placebo that used propranolol [38] in a small cohort of 21 patients. Authors showed a significant reduction of the agitation intensity (assessed by the Overt Aggression Scale) in the group treated with propranolol vs controls with a maximum effect obtained 5 weeks after treatment and no significant difference in the number of agitation episodes between the two groups. No major adverse events were reported in this study. Beyond this study, the main risk with beta-blockers use is a drop in arterial blood pressure and heart rate. Thus, the risk appears relatively limited for young patients, especially when the dose used is relatively low (below 80 mg per day).

Antiepileptic Drugs

Valproic acid (VPA) is commonly prescribed antiepileptic medication which is also used in the treatment and management of bipolar disorder, acute mania and migraines. Clinical trials have shown mixed results: in a retrospective chart review, agitation symptoms following TBI responded to VPA at doses equivalent to conventional psychiatric practice (1,250 mg/day) [39]. A double-masked, parallel group RCT found no adverse or therapeutic effects of VPA on neuropsychological functioning in patients with TBI [40]. Advantages of VPA, in addition to its possible unique efficacy, include a lower propensity towards sedation and cognitive impairment, and thus a more robust potential for rehabilitation participation [41]. Carbamazepine (CBZ) is another widely used anticonvulsant in the management of agitation and aggression in TBI. A study found that CBZ at doses ranging from 400 to 800 mg per day reduced irritability and disinhibition [42]. However, a Cochrane review revealed that even though CBZ is often the drug of choice in managing aggressive behaviours following brain injury there is a lack of large RCTs supporting its effectiveness [43].

Antipsychotics and Neuroleptics

Widely used in the past in the treatment of ICU-related delirium, haloperidol effectiveness is now questioned because of two recent placebo-controlled RCTs which found no evidence to suggest an impact on the prevalence or duration of delirium in critically ill patients needing mechanical ventilation [29,44,45]. In recent years, atypical antipsychotics have gained increasing popularity. These include risperidone, olanzapine, quetiapine, and ziprasidone, all of which has been found to be beneficial in the treatment of delirium [46]. Quetiapine may provide quicker PTD-related symptoms resolution, fewer episodes of agitation and a greater rate of transfer to home or to rehabilitation [47). Neuroleptic use, especially typical agents, can present risk of extrapyramidal symptoms, restlessness, tardive dyskinesia and prolongation of the QT interval which can precipitate fatal arrhythmias in vulnerable individuals.

Methylphenidate and Donepezil

Methylphenidate is another psychostimulant that is widely used in the treatment of attention deficit hyperactivity disorder. Evidence from stroke studies suggest that methylphenidate induces modulation of cerebral activation and promotes normalization in cognitive neuronal network along with plasticity to improve motor performance. In a double-blind, placebo-controlled RCT in TBI patients, methylphenidate was found to have clinically significant positive effects on speed of processing and caregiver ratings of attention [48]. In most studies, methylphenidate was administered twice daily (fixed dose of 10 to 15 mg or at a dose of 0.3 mg/kg). A randomised trial showed that Donepezil improved short-term memory and sustained attention in patients with acute PTD [49].

Conclusion

The pathophysiology of PTD is not completely understood but its substrate is a combination of structural damage and functional disturbances mediated by inflammation and neurotransmitter imbalance. Cognitive impairment and behavioural changes often present themselves in the acute phase following severe TBI and result in long-term disability in a significant percentage of patients. Other manifestations of structural damage and functional imbalance following TBI include post-traumatic seizures (PTS) and an increased risk to develop neurodegenerative disorders such as Alzheimer disease (AD), chronic traumatic encephalopathy (CTE), and amyotrophic lateral sclerosis (ALS) in later stages of life. Due to the presence of underlying structural damage, the functional and potentially treatable component of PTD may be under-recognized and go undertreated. Although a variety of therapeutic strategies have been proposed, there remains a lack of robust evidence to support a standardised approach to diagnosis, prognostication and treatment of PTD.

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Titles of Tables

Table 1. Non-pharmacological measures used in the prevention of delirium in ICU.

Table 2. Pharmacological agents used in the treatment of acute delirium in ICU (AEDs – Anti Epileptic Drugs).

Titles of Figures

Figure 1. Pathophysiological mechanism hypothesized to play a role in the development and progression of delirium in critically ill patients (CNS – Central Nervous System).

Table 1. Tools used in the diagnosis of ICU delirium in neurocritically ill patients.

Methods	**Tools**	***Notes/Biomarkers***
Clinical	Confusion Assessment Method for the ICU (CAM-ICU) Intensive Care Delirium Screening Checklist (ICDSC) Richmond Area Sedation Scale (RASS) Sedation-Agitation Scale (SAS)	• *CAM-ICU and ICDSC has been used in neurocritical care patients to diagnose delirium* • *Sedation for neurocritical care patients is neuroprotective yet it may confound neurological assessment*
Electroencephalography	Raw EEG Spectrum analysis Sleep studies	• *Generalized slowing (theta and delta rhythms)* • *Dropout of the posterior dominant rhythm, poor organization of the background rhythm, loss of reactivity* • *Reduced fast-to-slow band power ratio, reduced mean frequency, and reduced occipital peak frequency* • *Differential diagnosis with seizures* • *Association between sleep deprivation, disturbed circadian rhythm and ICU delirium*
Neuroimaging	Structural imaging (CT, MRI, DTI)	• *Mild diffuse axonal without focal damage frequently associated with attentional deficit* • *Fronto-temporal damage (contusions, haemorrhages, or white matter damage) could result in amnesia* • *Attention impairment due to long-range cortico-cortical connections supporting large-scale brain networks* • *Limbic system damage with irritability, quickness to anger, disinhibition, or emotional* • *Right para-hippocampal region and parietal lobe damage causes acute delirium*

Table 2. Neuro-pharmacological agents currently used in the treatment of acute delirium in ICU and in the subacute rehabilitation phase.

Class	**Agent**	**Acute phase**	**Rehabilitation**	***Notes***
α-agonists	Clonidine Dexmedetomidine	+ +		• *Effective for agitation associated with opioid withdrawal syndrome* • *Alternative sedative agent in ICU*
Benzodiazepines	Lorazepam Diazepam Midazolam	+ + +	+ +	• *Associated with worse delirium symptoms in general ICU* • *Used in alcohol and benzodiazepine withdrawal syndrome*
B-blockers	Propranolol		+	• *Effective after long treatment (5 weeks)*
Anti-Epileptic Agents	Valproic Acid Carbamazepine		+ +	• *Less sedation* • *Effect on irritability and disinhibition*
Antipsychotics and Neuroleptics	Haloperidol Risperidone Olanzapine Quetiapine Ziprasidone	+ + + + +	+ + + +	• *Not recommended to prevent delirium* • *QT interval prolongation* • *Exacerbation of extrapyramidal symptoms*
Antidepressants	Fluoxetine		+	• *Improved motor function and increased activity in the motor cortex*
Psychostimulants	Methylphenidate Amantidine Donepezil Dexamphetamine		+ + + +	• *Modulation of cerebral activation* • *Improved plasticity and recovery* • *Improved short-term memory* • *Improved motor recovery*

Table 3. Future key research areas in ICU delirium and post-traumatic agitation.

Themes	**Topic**	***Wider research questions***
Epidemiology	Incidence Features and Definition	• *What is the incidence of PTD in TBI patients?* • *How do we better define the continuum of cognitive and consciousness disorders in the acute phase after TBI?*
Pathophysiology	Neuroinflammation Neurotransmitters Networkpathy	• *What are the neuroinflammatory mechanisms underpinning PTD?* • *What neuronal and astrocytic molecular targets play a pivotal role in the development of PTD?* • *What type of brain injury and what network lesions are hierarchically more associated with PTD?* • *Is there a genetic predisposition towards neurocognitive dysfunction in patients who develop PTD?*
Diagnosis	Clinical Structural Functional	• *What is the best assessment to discriminate neurological deficit from functional cognitive impairment?* • *What methodology best discriminates and identifies the pathophysiology mechanism associated with PTD?* • *How do the functional PTD features change over time?* • *Could a machine-learning classifier identify early patients at risk of PTD?*
Treatment	Sedation Neuroinflammation Neurotransmitters	• *What neuroprotective sedation strategy is more effective to prevent PTD?* • *Are anti-inflammatory agents effective effective in preventing/treating PTD? What agents are more effective?* • *What neuropharmacological agents are more effective to modulate neurotransmission and prevent/treat PTD?* • *What behavioural cognitive techniques are effective in the acute and subacute phase of PTD?* • *Are there effective physical neuromodulation techniques available to treat PTD?*
Prognosis and long-term effects	Prognosis Long-term cognitive outcome	• *What is the ideal model/classifier to stratify patients at risk of PTD?* • *What are the long-term cognitive effects of PTD?*

NEUROTRASMITTERS PATHWAYS: