NEUROPSYCHIATRIC DISORDERS AFTER TRAUMATIC BRAIN INJURY: A REVIEW

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ABSTRACT
Traumatic brain injury is a significant public health concern. Neuropsychiatric complications are more prevalent and persistent for a long time in brain injury patients than general population. This review highlights the close link between traumatic brain injury and neuropsychiatric changes and provides an overview of prevalence, clinical findings, aetiology and treatment of psychiatric sequelae including mood disorders, anxiety disorders, aggression, cognitive deficits, psychosis, personality changes and post-concussion syndrome following brain injury.

KEYWORDS: Traumatic Brain Injury, Neuropsychiatric Complications, Mood Disorders, Cognitive Deficits, Psychosis, Post-Concussion Syndrome

INTRODUCTION
Traumatic brain injury (TBI) is universal and extremely major public health problem. A position statement by the International and Interagency Initiative toward Common Data Elements for Research on Traumatic Brain Injury and Psychological Health (Menon et al., 2010) states that “TBI is an alteration in brain function, or other evidence of brain pathology, caused by an external force”. A report of Centers for Disease Control and Prevention showed that there were 1.7 million TBI’s patients in the United States between 2002-2006 (Faul et al., 2010). Out of them, 1.3 million attended accident departments; 2,75,000 were hospitalised and 51,000 died. In India, approximately 1.5-2 million peoples are injured and 1 million succumb to death annually. Road traffic injuries are the major contributing cause (60%) of TBI. Violence (10%) and falls (20-25%) are the other causes of brain injury (Gururaj 2002; Puvanchandra and Hyder, 2009). The majority of the injuries about 85% are mild in nature (Bazarian et al., 2005). Children aged to 4 years, adolescents (15-19 years) and older adults (> 75 years) are more likely to sustain a TBI (Centres for Disease Control and Prevention, 2010). Traumatic brain injury causes variety of deficits. Despite the physical deficits at early stages of recovery from severe brain injury, numerous psychiatric deficits contribute to the
major morbidity leads to impairment in the capacity to return to work and social activities of patients (Deb et al., 1999).

Due to the number of reasons, neuropsychiatric disorders following TBI are important to be considered. Firstly, brain injury in most of the cases leads to permanent disability after trauma. These injuries occur most frequently in young individuals and the cost utilized during their treatment, maintenance and rehabilitation both to individuals and society is enormous (Jennet, 1996). Secondly, the psychiatric complications of brain injury may frequently be overlooked and under-treated. But the peoples with the mild injury do not receive adequate follow up care (Feinstein and Rapport, 2000). Due to the improvement in clinical management of brain injury, the mortality rate has been significantly decline. However the patients survived after TBI will possess various psychiatric complications and need neuropsychiatric management years after the injury. It is therefore necessary to increase understanding and clarification about the psychiatric findings after the injury so that psychiatric management is planned as early as possible for improving functions and limiting disability. In this article, we briefly review various neuropsychiatric disorders after brain injury.

**Relationship between pathology of TBI and occurrence of neuropsychiatric disorders**

**Risk factors for neuropsychiatric disorders**

Along with injury severity, there are many factors which involved in the aetiology of neuropsychiatric symptoms after brain injury.

**Pre-injury Constitutional factors:** These factors include socio-economic status, psychiatry history, forensic history, alcohol misuse and length of education having an impact on psychiatric outcomes after brain injury.

**Post-injury factors:** These factors include environmental and social difficulties, particularly, in those who have cognitive impairments, financial difficulties, occupational problems and threats to personal and family safety after injury produces the significant effect on psychiatric disorders after brain injury.

Premorbid personality traits (Corrigan et al., 1998; Hall et al., 1998; Tate, 1998), age and arteriosclerosis are the other factors that delay the reparative process within the central nervous system (Leishman, 1998). Similarly, marital discord, poor interpersonal relationship, or problems at work important contributors to the poor psychiatric outcome (Rao and Lyketsos, 2000).
This Relationship is Summarised in Fig.1.

Fig.1: Schematic presentation of relationship between pathology of TBI and neuropsychiatric disorders.
Neuropsychiatric disorders after TBI

1. Mood disorders
   a. Major depression

   **Prevalence:** It is frequent and common complication of TBI that produces a deleterious effect on recovery process of brain injured patients (Jorge et al., 2004). The prevalence rate for major depressive disorder is between 15-60% (Kim et al., 2007; Jorge et al., 2004).

   **Clinical findings:** The symptoms of post-TBI depression do not differ from those patients having depression without head injury although patients with head injury are characterised by irritability, anger and aggression than by sadness (Reeves and Panguluri, 2011). It is associated with executive dysfunction, feeling of loss, demoralisation and discouragement soon after the injury and then followed by persistent dysphoria and suicidal thoughts (Rappport et al., 2003). Fatigue, irritability, disinterest and insomnia are seen after long time period i.e. 6-24 months after head injury. Psychological impairment in excess of the severity of injury and poor co-operation with rehabilitation are strong indicators of a persistent depressive disorder (Kraus, 1999). After the period of initial recovery, erratic or poor recovery or worsening of neurological deficits may be the signs of depression.

   **Aetiology:** Depression may be occurring after TBI of any severity. Several studies have shown an association between post-TBI depression and lesions in the left dorsolateral prefrontal cortex and left basal ganglia in the acute phases of TBI (Fedoroff et al., 1992). Jorge and colleagues (2004) found a decrease in the left prefrontal grey matter volume, especially in the ventrolateral and dorsolateral regions in patients with post-TBI depression. It has been found that damage to the neuronal circuits in prefrontal cortex, amygdale, hippocampus, basal ganglia and thalamus may be related to the development of depressive symptoms after TBI. Rupturing of the biogenic amines containing neurons, which pass through the basal ganglia or frontal subcortical white matter, may be responsible for the development of depression due to TBI (Chaudhury et al., 2005).

   **Treatment:** Selective serotonin reuptake inhibitors (SSRIs) are used as first line drug therapy for the treatment of post-TBI depression because they are safe and well tolerated (Fann et al., 2009). Tricyclic antidepressants, dopaminergic agents and psychostimulants are used as second line drugs because of their side effects (Gualtieri and Evans, 1988; Kraus 1995). Electroconvulsive therapy is used a viable option for refractory patients (Ruedrich et al., 1983).
b. Mania

Prevalence: TBI is responsible for the generation of both unipolar mania and bipolar disorder (Mortensen et al., 2003). Mania is usually less common than post-TBI depression. Reekum and colleagues (2000) found a prevalence of 4.2% for mania directly caused by TBI.

Clinical findings: The symptoms of mania after TBI are more aggression, irritability, less euphoria, changes in mood, impulsivity and even violent behaviour. About 50% of the post traumatic mania patients have abnormal EEG (Chaudhury et al., 2005).

Aetiology: It has been found that a co-relation exists between mania occurrence and severity of TBI. Hypomania and bipolar II disorder have been found in mild traumatic brain injury patients whereas chronic mania, bipolar I and schizoaffective disorder associated with severe trauma. However, these studies conflicts with the observation of Jorge and colleagues (1993) who represents that there is no co-relation exists between severity of trauma and mania. Post-TBI mania may be associated with multifocal brain lesions primarily in temporal basal poles and secondarily the lesions in right sided limbic or limbic related structures (Jorge et al., 1993).

Treatment: There is little evidence in the literature for the treatment of post-TBI mania. Mood stabilising antiepileptic drugs such as carbamazepine and valproic acid are used as first line treatment (Kile et al., 2007). Atypical antipsychotics can also be used if patients having psychotic features also. Lithium carbonate should be avoided because it lowers seizure threshold, worsen cognitive impairment and having low therapeutic index (Kraus, 1999).

2. Anxiety disorders

There are various types of anxiety disorders occurs after TBI such as generalised anxiety disorder (GAD), phobic disorders, post-traumatic stress disorder (PTSD) and obsessive compulsive disorder (OCD) in which PTSD is more common. The range of frequency of all anxiety disorder is 11-70% (Lewis, 1942; Klonoff, 1971).

a. Post-traumatic stress disorder

Prevalence: The most commonly and frequently studied anxiety disorder associated with TBI is PTSD. The prevalence rate of PTSD is 3-27%.
Clinical findings: Mayou et al (1993) suggested that PTSD is “not associated with a neurotic predisposition” but is “strongly associated with horrific memories of the accident”. It is also characterised by re-experiencing of the traumatic events through nightmares and intrusive thoughts.

Aetiology: Researches do not found consistent reports which contribute to the identification of specific brain lesion in the development of PTSD after TBI. Sojka and colleagues (2006) found a positive co-relation between the serum level of cortisol (a biochemical marker of stress), S-100 B and neural specific enolase (two biochemical marker of brain injury) in acute phase of mild TBI and occurrence of PTSD one year later. Bryant investigated that patients having amnesia at the moment of injury can re-experience vivid pseudomemories of the event generated through a combination of imagination and information learnt following trauma (Bryant, 1996). Therefore, it is possible that some of the traumatic event is code even during the period of consciousness disturbances. Acute stress disorder is an important contributor for the subsequent development of PTSD (Harvey and Bryant, 2000). Mild head injury patients who experience acute stress disorder earlier (1 month post injury) having 82% of prevalence rate of PTSD as compared to those who did not suffer acute stress disorder having 11% prevalence rate (Bryant and Harvey, 1998).

Treatment: SSRIs, Venalafaxine, opioid antagonists such as naltrexone (Tennant, 1987) and buspirone (Gualiteri, 1988) are used as promising treatment of PTSD. Benzodiazepines (Prestone et al., 1989) and antipsychotics (Feeney et al., 1982) should be avoided as they cause cognitive impairment, disinhibition and delayed neuronal recovery. Non-pharmacological treatment such as cognitive behavioural therapy (CBT), neurohabilitation and psychotherapy are important in treatment of PTSD (Soo and Tate, 2007).

3. Aggression

Prevalence: Aggression is a common, frequent and challenging neuropsychiatric complication of TBI (Baguely et al., 2006). Various associated terms such as irritability, anger and agitation have been used in the context of aggression (Schwarzbold et al., 2006). 35-96% of the post-TBI patients are reported to show aggressive behaviour in the acute phase of the injury (Reeves and Panguluri, 2011). In most of the cases, aggressive behaviour resolves but it may also contribute to the chronic phase and long term aggression is a
common psychiatric consequence of TBI (Fleminger, 2010). Tateno and colleagues showed that 33.7% patients exhibited aggressive behaviour within first 6 months of injury and 25% patients at 6, 24 and 60 months also displaying aggressive behaviour (Baguely et al., 2006).

Clinical findings: Aggression includes externally directed acts (e.g. verbal outbursts, physical violence towards objects and persons) as well as self-directed violence (e.g. non-suicidal self-directed violence, suicide attempts and suicide). This aggressive behaviour interferes with rehabilitation efforts, disrupts social support networks and delay in optimal recovery (Wortzel and Arciniegias, 2013). Aggression raises the critical safety concern. Recent studies suggested a positive relationship between TBI and self-directed violence such as suicide (Simpson and Tate, 2007; Simpson and Tate 2007; Wasserman et al., 2008; Brenner et al., 2011).

Aetiology: Post-traumatic aggression is generally associated with frontal lobe lesion (Wortzel and Arciniegias, 2013). The frontal and temporal lobes are highly prone to the deleterious effects of contact and inertial forces to which brain is subjected during biomechanical trauma (Gurdjian, 1995; Povlishock and Kartz, 2005; Bigler, 2007). The white matter of the brain stem, cerebral parasagittal, corpus callosum and grey-white junctions of the cerebral cortex is also injured by TBI (Gennarelli, 1993; Meythaler et al., 2001; Povlishock and Kartz, 2005; Bigler, 2007). Emotional aggressive behaviour is regulated by a complex circuit consisting of the orbital frontal cortex, amygdale, anterior cingulated cortex and several other interconnected regions (Davidson et al., 2000). It is suggested that damage to the prefrontal cortex resulting in loss of self control with spontaneous aggressive and violent behaviour (Graftman et al., 1996). TBI also disrupts the major modulatory neurotransmitters systems such as cholinergic, dopaminergic, noradrenergic and serotonergic projection which may be responsible for the disturbances in frontally mediated cognition, emotion and behaviour (Wortzel and Arciniegias, 2013).

Treatment: Non-pharmacological interventions are often preferred over the drug therapies. After the failure of environmental interventions and in the later stages of recovery, pharmacological treatments are considered (Lombard and Zafonate, 2005). Beta-blockers such as propanolol and pindolol, anti-convulsants such as carbamazepine and pindolol,
antipsychotics, antidepressants, buspirone, lithium and amantadine have been used to manage post traumatic aggression.

4. Cognitive disorders

Prevalence: Transient and persistent cognitive deficits are more common after brain injury (McAllister, 2008). The prevalence rate of cognitive deficits is 25-70% after TBI (Vaishnavi et al., 2009). The focal and diffuse brain injury produces cumulative deleterious effects on the cognitive ability of the persons. Cognitive impairment depend on a number of factors such as degree of diffuse axonal injury, duration of loss of consciousness and post traumatic amnesia, brain stem dysfunction and the size of focal hemispheric injury (Chaudhury et al., 2005).

Clinical findings: After the occurrence of TBI, there is immediate loss of consciousness or coma may ensue followed by a variety of changes have been occurred. Disturbances in executive functioning such as poor planning, organizing sequencing, impaired judgement and impulse control, impairment of alertness, increased lapses of attention, memory deficits, impaired figure ground perception and constructional abilities, anomia and word finding difficulties, aphasia and reduction in performance and verbal IQ have been seen after brain injury (McCunyn and Russo, 1984; Levin et al., 1990; Jones et al., 1996; Menon and Rao, 1997; Dockree et al., 2004). Long term studies have found that in most of the patients cognitive functions continue to improve or deteriorate for many years after the injury (Millar et al., 2003; Hammond et al., 2004).

Aetiology: Cognitive impairments are directly related to the severity of injury (Fleminger, 2008). TBI can result to a progressive neurodegeneration known as traumatic encephalopathy (dementia pugilistica/punch drunk syndrome) (Gavett et al., 2010). This syndrome includes cerebellar, pyramidal and extrapyramidal features, mixed cortical and subcortical cognitive deficits and a variety of behavioural symptoms. Chronic traumatic encephalopathy can produce cognitive symptoms alone or in conjunction with other neurodegenerative processes such as Alzheimer’s disease (Gavett et al., 2010).

Treatment: A multidisciplinary approach has been adopted for the treatment of these cognitive disorders. Specific cognitive deficits may improve through occupational therapy, physiotherapy, speech therapy, vocational therapy, cognitive rehabilitation and
pharmacological interventions (Arciniegas et al., 2010). TBI leads to decrease in dopaminergic activity and a hypocholinergic state (Writer and Schillerstrom, 2009). Agents such as methylphenidate which increasing the level of dopamine in brain may have positive role in the restoration of cognitive processing (Neurobehavioural Guidelines Working Group, 2006; Kile et al., 2007). Non-stimulants dopamine enhancers such as bromocriptine, amantadine, pramipexole and levodopa improve cognitive impairments. Memory and attention has been restored using acetylcholinesterase.

5. Psychosis

Prevalence: During the period of delirium after TBI, transient psychotic symptoms are not uncommon. The symptoms of the psychosis may be acute or chronic and transient or persistent after head injury. Davidson and Bagley (1969) concluded that between 0.07% and 9.8% of patients with TBI develop a post traumatic schizophrenia like psychosis. The prevalence rate has been increasing over time. Most of these patients do not have family history of schizophrenia. Men are found to be more affected by post-TBI psychosis than women (Fujii et al., 2002). The post head injury psychosis is the area of interest due to clinicians and neuroscientists due to the following reasons.

i. The long latency is usually found between TBI and psychotic symptoms so the appearance of psychosis is unexpected and puzzling.

ii. Some diagnostic issues are exists because some peoples having family history of psychosis, while many others do not.

iii. Psychosis has conceptual relevance to understandings schizophrenia spectrum disorder (Chaudhury et al., 2005). Short latencies are associated with diffuse injury whereas longer latencies due to focal damage to the brain.

Clinical findings: Immediately after TBI, the clinical features of delirium such as confusion, inattention, cerebral disorganisation are observed. After this phase, more discrete psychotic features might become evident with characteristics symptom include delusional disorientation, delusional misidentification and confabulation. The long term clinical symptoms are persecutory and other delusions, hallucinations, prodromal symptoms (depression, antisocial and inappropriate social withdrawal and deterioration at work (Sachdev et al., 2001; Fujii and Ahmed, 2002).
Aetiology: A direct causal association between TBI and psychosis is difficult to establish. Neuro imaging, EEG and lesion location techniques consistently report abnormalities in the temporal areas (Davidson and Bagley, 1969; Fujii and Ahmed, 2002). Some diagnostic techniques are also reported the abnormalities in the frontal lobes (Achte et al., 1991; Fujii and Ahmed, 2002). These findings occurred in equal occurrence in the left and right hemisphere.

Treatment: Atypical agents such as olanzapine are preferred over typical antipsychotics because they having less dopamine antagonism and greater serotonergic activation. The initial doses of these drugs should start low due to their side effects. Clozapine is not considered for treatment because it can lower seizure threshold and has anticholinergic properties that can further impairs cognitive functions and may provoke delirium.

6. Changes in personality

Prevalence: TBI can responsible for the significant changes in personality and emotional regulation. Pre-existing personality traits can become more pronounced, or the personality can be drastically altered. The most common categories of personality disorders are avoidant, borderline and paranoid (Hibbard et al., 2000; Koponen et al., 2002). 60% of the patients showing the post-TBI personality changes and the most prevalent type are apathetic, unstable, disinhibited and aggressive. Apathy is the most prevalent symptom occurring in 34.5% of the persons. Younger patients are found to be more susceptible to apathetic than older patients who are likely to be depressed.

Clinical findings: The cognitive and behavioural changes are directly correlates with severity of injury. The common symptoms observed are apathy, loss of spontaneity and drive, labile mood, self-centered behaviour, disinhibition, irritability, reduced control over aggressive impulses, excessive tiredness, inflexibility, tendency towards perserveration, a change in quality of relationship with more shallowness and obsessive compulsive disorder (Fleminger, 2008). Personality changes are one of the most distressing complications of TBI for families and carers.

Aetiology: TBI may cause isolated changes in personality with little or no effect on neuropsychological testing (Fleminger, 2008). The damage to the medial orbital surface of
the frontal lobes and the anterior inferior surface of the temporal lobes during TBI is responsible for the changes in personality. Two types of personality changes have been found due to frontal lobe injury.

i. **Pseudopsychotic changes:** These include euphoria, impulsiveness, inadequate action and disinhibition. These changes occur due to the lesions in the orbitobasal aspects of the frontal lobes.

ii. **Pseudodepressed changes:** These changes include narrowing of interest, generalised emotional indifference, general inhibition and torpidity. These changes occur to the lesions of the convexity regions of the frontal lobes.

Apathy has been associated with subcortical and right hemispheric injuries (Anderson et al., 1999). Cortico-striatalpallidal-thalamic pathways, encoding the anterior cingulated cortex, nucleus accumbens, ventral pallidum, and medial dorsal thalamic nucleus are considered mediators of motivation and damage to these circuits can produce apathy. Dopamine is the main neurotransmitters that involved in the occurrence of apathy (Schwarzbold et al., 2006).

**Treatment:** In non-pharmacological intervention, emotional support and education for the patients and family members is considered as most appropriate treatment (Kile et al., 2007; Vaishnavi et al., 2009). Cognitive behavioural therapy may also be helpful to the behavioural changes (Schwarzbold et al., 2008). In pharmacological intervention, SSRIs and mood stabilizers are used to treat the aggression and emotional instability (Kile et al., 2007).

7. **Post-concussion syndrome**

**Prevalence:** Mild head injury patients having persistent physical, cognitive and emotional symptoms referred to as post-concussion syndrome (PCS). The prevalence rate is 43% and a commonest neuropsychiatric complication after TBI in a prospective Indian study (Keshvan, 1981).

**Clinical findings:** The symptoms are headache, nausea, dizziness, unsteady gait, slurred speech, poor concentration, slowness in answering questions, memory and concentration problems, fatigue and weakness, visual disturbances, sensitivity to light and noise, tinnitus, periods of confusions or mental dullness and loss of self confidence (Ryan and Warden,
Most of the patients recover in 3-6 months after injury. About 15% of the patients will have symptoms lasting longer than 1 year.

**Aetiology:** The evidence of the current studies support the hypothesis that neurological factors play a greater role in the early phase of the syndrome but over the time psychological factors appear to become particularly relevant. In the neurological aspect, it is suggested that most of the pathology of concussion occurs following acceleration and deceleration forces leads to neural system dysfunction subset of patients with presumed PCS have been shown to have abnormalities on Positron Emission Tomography (PET) and Single Positron Emission Computed Tomography (SPECT) (Abu-Judeh et al., 1999; Chen et al., 2003). Patients having the symptoms of depression, anxiety and PTSD at 7-10 days post mild TBI predict PCS 3-6 months later.

**Treatment:** Non-pharmacological treatment preferred over the pharmacological interventions. In the early phases of the injury, educational information found to be effective. Psychotherapy, occupational and vocational intervention and social skills training are adopted to overcome the changes occur in the later phases of the PCS (Borg et al., 2004). CBT may also effective (Sayegh et al., 2010).

**Conclusion**

Patients suffering from TBI are often stated as “the walking wounded” because most of these patients have transient or persistent and acute or chronic neuropsychiatric disorder. Due to these complications, they are disabled personally, socially and occupationally, although they appear physically “normal”. The deleterious effects of these neuropsychiatric sequelae require immediate treatment. Ideally, treatment of these patients involves a multidisciplinary approach such as non-pharmacological and pharmacological interventions. For the best results, a neuropsychiatric working in close collaboration with the patient, family, neurosurgeon, social worker and the staff of a community groups.

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