Extracranial Complications of Traumatic Brain Injury: Pathophysiology—A Review

Parameswara Gundappa[1]

[1]Department of Anaesthesiology, Manipal Hospital, Bengaluru, Karnataka, India

Address for correspondence Parameswara Gundappa, MD, FICA, Department of Anaesthesiology, Manipal Hospital, 98, HAL Airport Road, Bengaluru 560017, Karnataka, India (e-mail: paramgundappa@gmail.com).

J Neuroanaesthesiol Crit Care 2019;6:200–212

Abstract

Moderate to severe traumatic brain injury is often associated with several extracranial organ complications, which increase the morbidity and mortality. Respiratory complications such as acute lung injury, pneumonia, and acute respiratory distress syndrome (ARDS) occur most commonly, but neurogenic pulmonary edema can be life threatening. Cardiovascular complications occur frequently. However, arrhythmia, cardiogenic shock, and neurogenic stunned myocardium, though occur infrequently, can be life threatening. Coagulation abnormalities and sepsis constitute serious complications that may result in multiorgan failure. These constitute independent risk factors for mortality. Endocrine abnormalities, gastrointestinal disruptions, and other complications occur less commonly. These extracranial complications develop as a result of altered neurogenic immune response, both central and peripheral responses. Brain tissue injury releases both proinflammatory mediators taking part in tissue reparative process and anti-inflammatory cytokines that propagate inflammation. In addition, release of massive amount of catecholamines after head injury results in proliferation of myeloid depressor cells in the circulation, release of reactive oxygen species, and release of immature neutrophils into the circulation. These anti-inflammatory mediators by complex mechanisms inhibit and decrease the number of T cells and cause apoptosis. This results in decreased production and release of cytokines and reduced lymphocyte activated killer cell cytotoxicity, resulting in impaired hypersensitivity reaction. Finally, the complex interplay of various factors leads to suppression of peripheral immune response and susceptibility for infection and sepsis, and causes extracranial organ system failure with increased morbidity and mortality.

Keywords
- extra cranial complications
- traumatic brain injury
- neurogenic pulmonary edema
- sepsis
- coagulation abnormalities
- neurogenic immune response
- peripheral immune suppression
- neurogenic stunned myocardium

Introduction

India has a very high incidence of road accidents. Every year more than 1.5 lakh people get injured in road traffic accidents, with a case fatality rate of 18%. Shekhar et al[1] in their study reported that about 60% of road accidents in India result in traumatic brain injury (TBI), with an overall mortality rate of 29%.[1] In a recent study by Kamal et al,[2] out of 1,527 patients with moderate to severe TBI admitted to All India Institute of Medical Sciences, New Delhi, mortality was 34% and remaining 67% had an unfavorable outcome at 6 months.[2] Mortality due to TBI is often related to direct injury to the brain and its consequences of increased intracranial pressure (ICP), contusions, hemorrhages, or diffuse injuries. Nevertheless, a significant number of patients with TBI develop systemic complications such as of respiratory, cardiac, renal, and other systems. These extracranial complications (ECCs) increase the morbidity as well as mortality of TBI.

Several studies have shown that TBI results in systemic extracranial injuries that may complicate brain injury.[2-4] It is interesting and imperative to understand why and how brain injury causes extracranial systemic involvement. This review discusses the various ECCs due to TBI and pathophysiology involved in the development of these complications.

received
November 6, 2018
accepted after revision
April 15, 2019
published online
July 14, 2019

DOI https://doi.org/10.1055/s-0039-1692883
ISSN 2348-0548.

Table 1 Extracranial complications related to brain injury

Respiratory complications	Acute lung injury Acute respiratory distress syndrome Pulmonary edema Pneumonia Atelectasis Aspiration pneumonitis
Cardiovascular complications	Hypotension Hypertension Arrhythmias Shock Neurogenic stunned myocardium (Takotsubo's cardiomyopathy)
Renal complications	Acute kidney injury
Gastrointestinal complications	Cushing's ulcers Ileus
Hematologic complications	Platelet dysfunction Coagulopathy
Infections	Sepsis and septic shock
Endocrine complications	Electrolyte imbalances Syndrome of inappropriate antidiuretic hormone secretion Cerebral salt-wasting syndrome Hypopituitarism Hypoadrenalism Hypothyroidism
Metabolic derangements	Hypoglycemia Hyperglycemia Hyperthermia

Treatment of these complications is beyond the scope of this review. Various systemic complications reported due to TBI are given in ►**Table 1**.

One of the earliest clinical studies on ECC was reported by Piek et al in 1992.[3] In their analysis of 734 patient records from Traumatic Data Bank, there were 1,709 ECCs. In a similar retrospective study by Schirmer-Mikalsen et al,[4] 133 case records of patients with only TBI were studied. Pneumonia was diagnosed in 71% and acute lung injury (ALI)/adult respiratory distress syndrome (ARDS) in 26% patients. Other complications such as severe sepsis (6%), renal failure (1.5%), and a coagulation disorder (6%) were the major ECCs. Age, Glasgow coma scale (GCS), hypotension during the first day of treatment, elevated blood sugar, and low albumin predicted an unfavorable outcome. Corral et al,[5] in their retrospective observational cohort study of TBI, analyzed data of 224 patients admitted to intensive care unit (ICU), with GCS < 9 for neurological and non-neurological complications and their impact on mortality.

Even though the reported incidence of different complications varies between these above studies, the major complications reported were sepsis (10–75%) and septic shock (6–8%), followed by respiratory infections, including pneumonia (28–68%), respiratory failure (41%), ALI, and ARDS (9–28%). Cardiovascular complications were hypotension (20–44%), hypertension (12%), and requirement of vasopressors (70%). Coagulopathy (6–27%), electrolyte disturbances (21–59%), and acute renal failure (1.5–8%) were other systemic complications. Statistically significant mortality was reported due to ARDS (90%), hypoxia (69%), septic shock (85%), bleeding complications (50%), acute kidney injury (AKI) (76%), and non-neurological surgery (21%). Respiratory and cardiovascular complications were the most common early complications occurring within 3 to 4 days, with pneumonia (40.6%) and septicemia (10%) occurring in the next 5 to 10 days. Gastrointestinal, renal, and hepatic complications were late complications occurring beyond second week. Other less common complications were low serum albumin (31%), hyperthermia (24%), and anemia (22%). Whereas GCS 3 to 5 and intracranial hypertension were neurological variables associated with mortality directly due to TBI, age, pulmonary complications, coagulopathy, AKI, and septicemia were found to be independent predictors of mortality. Non-neurological surgeries also increased the mortality in ICU. Other non-neurological complications increased the length of stay and morbidity in ICU but did not increase the mortality. The overall mortality related to extracranial organ dysfunction varied between 26 and 35%.

In a prospective observational cohort study, Zygun et al[6-8] combined trauma service data with ICU data, to study the incidence of non-neurological organ dysfunction in patients admitted to ICU. Maximum modified multiple organ dysfunction (MOD) score of ≥ 3 was considered as having organ dysfunction. Nearly 10% of patients under trauma service data had severe head injury admitted to ICU, and 89% of these patients developed ECC of at least one organ. Respiratory dysfunction was the most common complication (81%) with respiratory failure (23%) followed by cardiovascular dysfunction (52%) with cardiac failure (18%). Coagulation abnormalities (17%) with coagulation failure (4%) and renal dysfunction (8%) were less common complications. The overall mortality in their study was 32%. Mortality was independently associated with MOD score and worst GCS. Extracranial injuries with high Abbreviated Injury Score (AIS) were also associated with higher ICU mortality, emphasizing the importance of extracranial injuries in worsening TBI mortality. However, the timing of organ dysfunction did not influence the mortality. Sequential Organ Failure Assessment (SOFA) scoring system was found to be superior to MOD score with respect to hospital mortality in relation to non-neurological complications.[9]

These and several other studies have shown that systemic organ dysfunction can occur with head injury even in the absence of systemic non-neurological injury. These extracranial systemic dysfunctions can occur either during acute or recovery phase and even in later period. No correlation between the severity of the TBI and systemic manifestations has been shown, with ECC occurring even in mild head injury.

Pathophysiology of Extracranial Non-neurological Systemic Complications

Severe head injury results in (1) primary brain injury directly related to primary impact and (2) secondary brain injury as a result of secondary effects of increased ICP and decreased cerebral perfusion pressure. In addition, TBI may result in many extracranial systemic injuries. The factors responsible

for development of this non-neurological systemic dysfunction are result of a complex interplay of multiple factors involving autonomic nervous system, neuroendocrine dysfunction, neuronal immune and inflammatory responses, systemic immune response, and biochemical cascades.[10]

Neural Immune Response to Injury

Cerebral injury has been shown to produce depression of systemic immune response. Various complex mechanisms have been proposed for this immunity depression due to interplay of many vasoactive mediators and activity of immunity-related cells.

The immune modulation of the brain to cellular injury includes release of pro- and anti-inflammatory mediators. Cytokines include chemokines, interferons, interleukins (IL), lymphokines, tumor necrosis factor (TNF). The proinflammatory cytokines include mediators such as interleukins (IL-1, IL-6, and TNF-α, IL-18), and anti-inflammatory cytokines include IL-10, and TGF-β (transforming growth factor-β). Chemokines that include IL-8 are chemotactic in nature and attract leukocytic and monocytic chemotactic proteins. Brain injury may result in cellular death and release of nuclear and mitochondrial damage-associated molecular patterns (DAMPs) such as mDNA, *N*-formyl peptides into the circulation through disrupted blood–-brain barrier. DAMP molecules can initiate and propagate noninfectious inflammation.

Head injury at the time of crash is associated with severe sympathetic stimulation associated with massive catecholamine release.[11,12] Both glucocorticoids and catecholamine release results in proliferation of myeloid-derived suppressor cells (MDSCs) present in the circulation. MDSCs are myeloid cell types that possess strong immunosuppressive activities. MDSCs interact with other immune cell types, including T cells, dendritic cells, macrophages, and natural killer cells (NK cells) to regulate their functions. MDSC release and suppress monocyte response and lymphopenia. In addition to release of MDSC, there is production of reactive oxygen species (ROS), which inhibit, decrease the number, or cause apoptosis of T cells and their function. This results in decreased production and release of cytokines and reduced lymphocyte activated killer cell cytotoxicity, resulting in impaired delayed hypersensitivity reaction.[13-15] All these mechanisms result in profound peripheral immune suppression[10,13] (►**Fig. 1**).

Another mechanism involved is that the glucocorticoids and catecholamine released due to brain injury result in granulopoiesis,[16] and immature neutrophils are released into the circulation. These immature neutrophils suppress T-cell function due to presence of CD10 and CD25 in them. ROS cause T-cell apoptosis. The net effect of these interplay of substances released results in lymphopenia and impaired hypersensitivity reaction and peripheral immune suppression.

Brain responds to peripheral immune response by three mechanisms via (1) the hypothalamic—pituitary–adrenal (HPA) axis, (2) sympathetic nervous system, and (3) parasympathetic nervous system. Through HPA axis, glucocorticoids inhibit proinflammatory cytokines and promote release of anti-inflammatory IL-4 and IL-10. They increase T-cell capacity to suppress macrophages, inhibit neutrophil phagocytosis, induce lymphocyte apoptosis, and downregulate antigen-containing monocytes.[10,13] Catecholamines released by sympathetic stimulation suppress β-adrenergic receptor–dependent neutrophil-generated ROS, proinflammatory cytokine production, and NK cells. They also enhance anti-inflammatory cytokines. Stimulation of β-adrenergic receptor influences differentiation of naive T cells to T2 and T1 cells. T1 and T2 cells are part of the immune system. T1 cells are proinflammatory and T2 are anti-inflammatory. When faced with a pathogenic attack, the body responds with a T1 response, which involves proinflammatory cytokines, along with other immune cells, allowing the body to kill invading organisms. Normally, the proinflammatory T1 response is balanced by anti-inflammatory T2 response. When the balance of T1/T2 cells favor anti-inflammatory response, it increases the susceptibility to infection, sepsis, and septic shock.[13,14] β-Adrenergic receptor antagonists have shown to reduce the risk of ischemia, enhance brain metabolism and oxygen consumption, and protect cardiovascular stability.[17,18] In addition to sympathetic system, parasympathetic system stimulation also has been shown to decrease the systemic inflammatory response by decreasing the secretion of proinflammatory cytokines such as TNF-α, IL-1, IL-6, and IL-18, without affecting the release of anti-inflammatory cytokine IL-10. This "cholinergic anti-inflammatory pathway" is more rapid and localized compared to diffuse anti-inflammatory property of the sympathetic system[10,13,19] (►**Fig. 2**).

The anti-inflammatory pathway related to all the three above mechanisms results in increased peripheral immune suppression and susceptibility for infection, particularly pneumonia and septicemia. Toxicity as a result of septic shock, in the presence of hypotension, cardiovascular collapse, hemorrhage, and coagulation abnormalities is responsible for development of systemic organ failure such as acute renal failure, hepatic failure, and other systemic complication.

Respiratory Complications

Respiratory complications are the most common ECCs after severe head injury, with their incidence varying from 28% to 65%.[3,4,6-8,20-22] The various complications are (1) neurogenic pulmonary edema (NPE), (2) ALI and ARDS, (3) pneumonia, and (4) lung collapse and atelectasis. Though these complications occur with definite symptoms and signs along with typical X-ray finding, subclinical changes such as ventilation-perfusion abnormalities, increase in respiratory resistance, and impairment in muscle function cause hypoxia of varying degree. These respiratory changes occur early after brain injury and constitute independent risk factors of mortality and account for > 50% of patients dying due to brain damage.[20-22]

These respiratory complications develop as a result of "double hit" mechanisms.[21,22] First, the "blast injury" due to severe sympathetic response and release of catecholamines after brain injury, and the second "systemic inflammatory responses" in the brain with the release of pro- and anti-inflammatory mediators released into the systemic circulation.

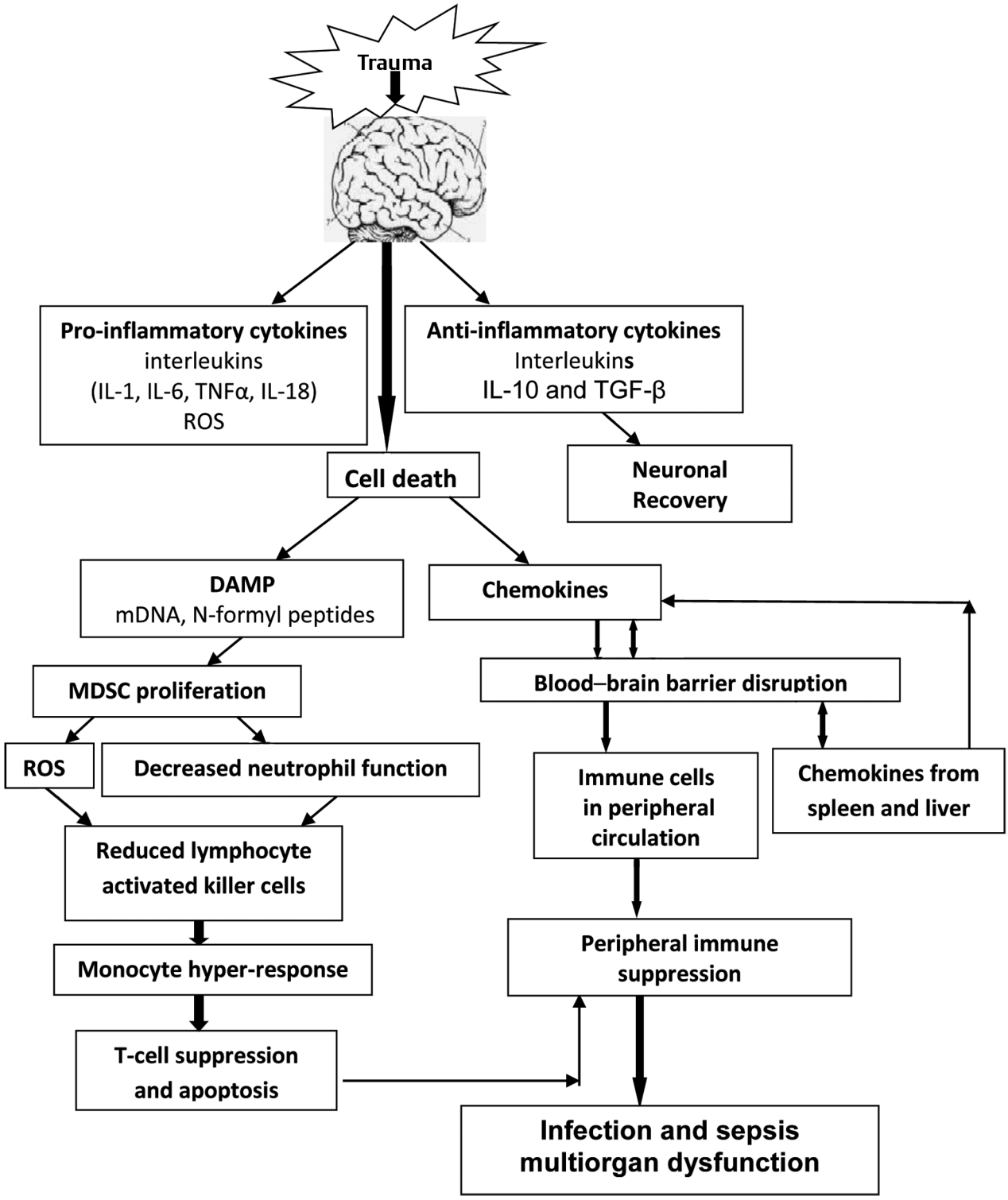

Fig. 1 Mechanism of immune suppression and multiorgan dysfunction due to traumatic brain injury. DAMP, nuclear and mitochondrial-associated molecular pattern; IL, interleukin; MDSC, myeloid-derived suppressor cell; ROS, reactive oxygen species; TGF-β, transforming growth factor-β; TNF-α, tumor necrosis factor-α.

Pulmonary Edema

Traumatic brain injury can result in abrupt increase in ICP leading to neuronal compression, ischemia, or damage, which is believed to give rise to an intense activation of the sympathetic nervous system and the release of catecholamines. The large amount of catecholamines released due to sympathetic storm caused by sudden and acute increase in ICP causes increase in intravascular pressure, systemic hypertension as well as pulmonary hypertension, and alveolar capillary membrane disruption. Extravasations of protei rich fluid from damaged alveolar-capillary membrane leads to

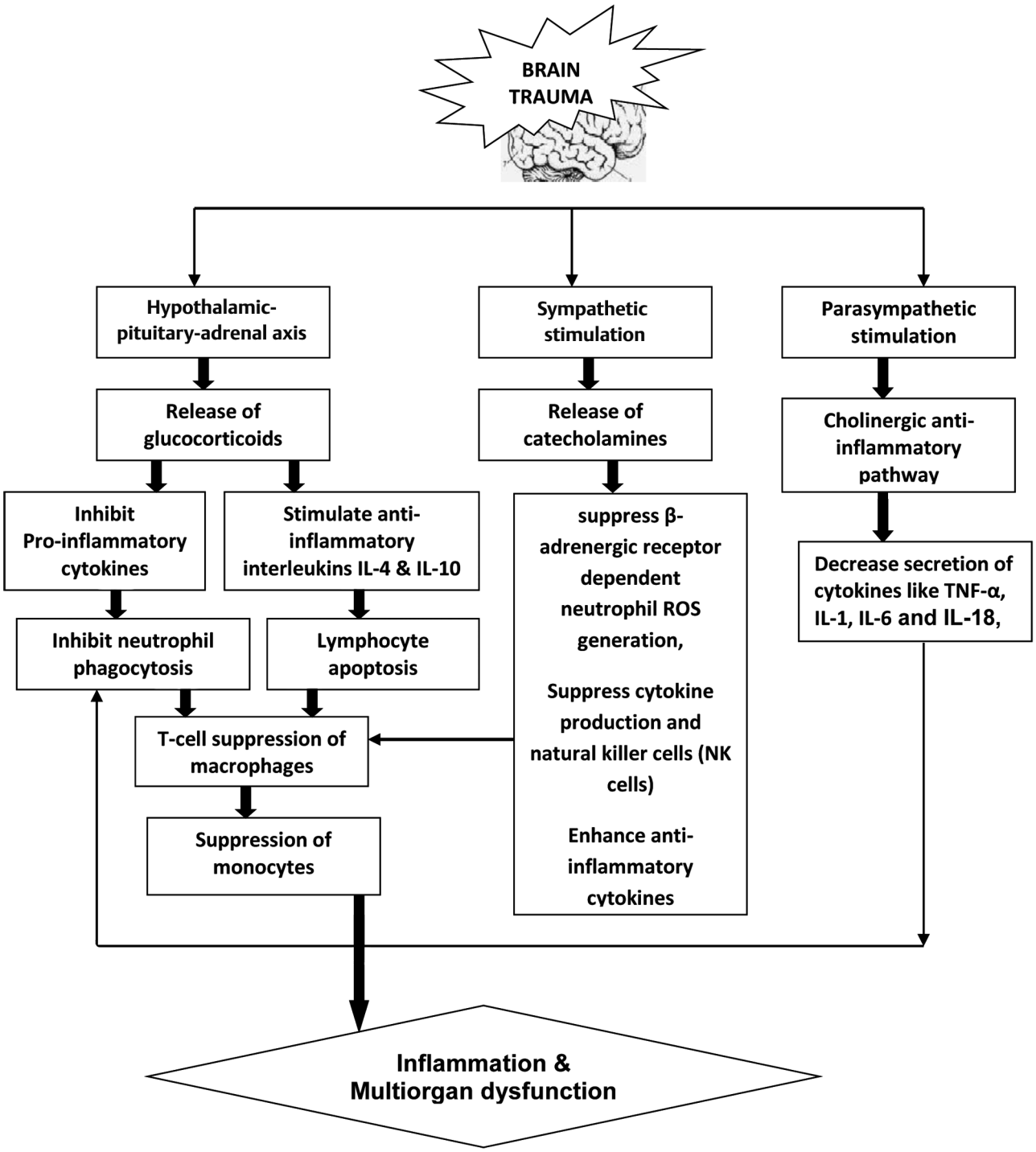

Fig. 2 Brain response to peripheral immune response. IL, interleukin; NK, natural killer; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α.

development of NPE.[23,24] This entity was first described by Shahanan[25] in epileptic patients and mechanism described by Theodore and Robin in head injury.[26] NPE differs from other types of pulmonary edema in that there is not only increase in capillary hydrostatic pressure but also increase in capillary permeability and accumulation of extravascular proteinaceous material (►**Fig. 3**). NPE generally occurs within 72 hours and is associated with high mortality (50%). The severity of NPE is related to severity of TBI and severity of ICP increase. However, those who survive NPE recover very quickly. Experimental data from rat studies have shown that pretreatment with α-adrenergic antagonist prevents the hypertensive response and decreases the severity of NPE and other respiratory complications.[27]

Acute Lung Injury and Acute Respiratory Distress Syndrome

Brain injury leads to production of pro-inflammatory mediators. The microglia and astrocytes release tissue cytokines,

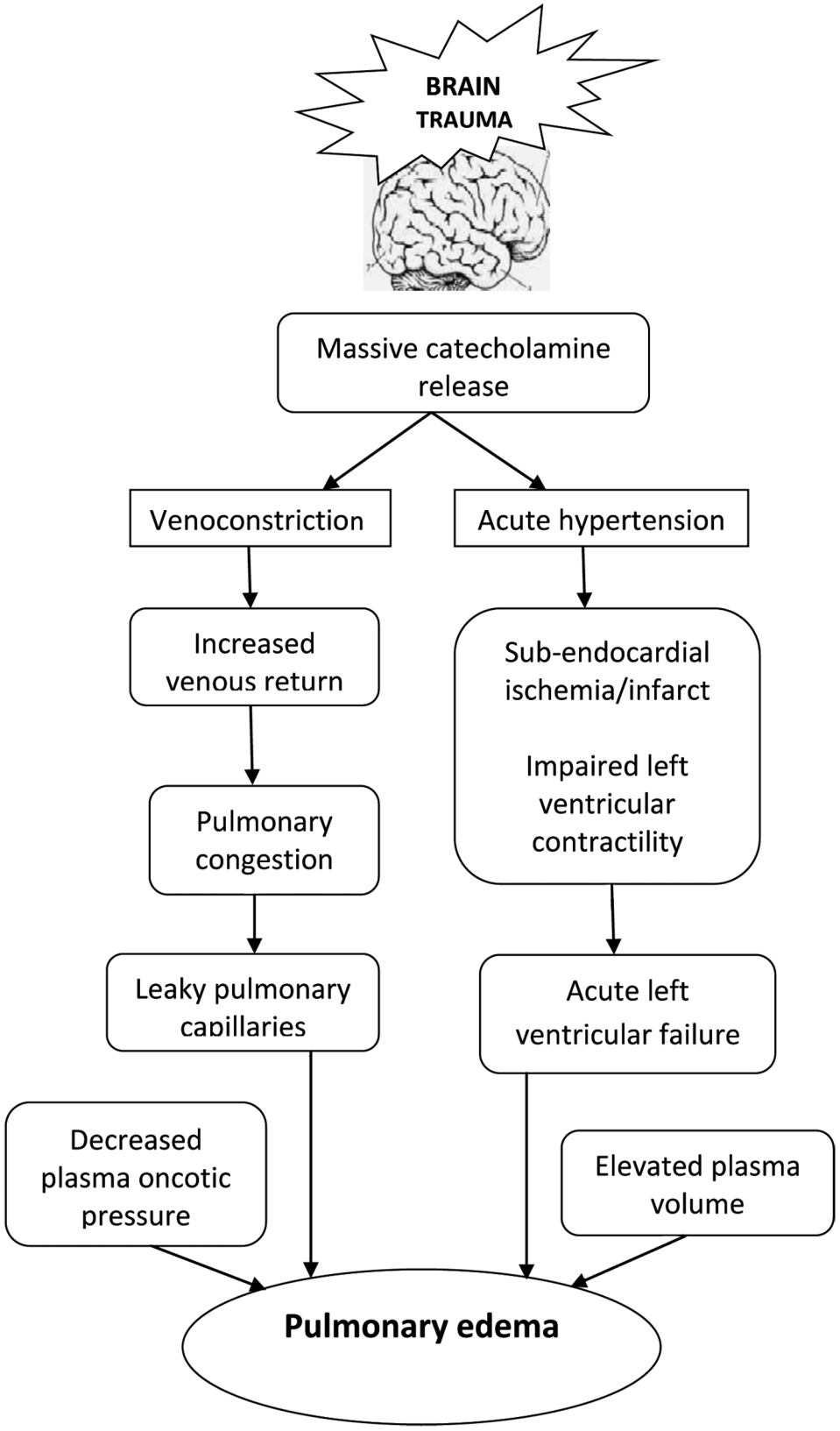

Fig. 3 Pathogenesis of neurogenic pulmonary edema.

IL-8, and other neurokinins. These inflammatory mediators cross disrupt the blood–-brain barrier into the systemic circulation and activate inflammatory cascade in the lungs and other peripheral tissues. Neutrophils and macrophages migrate into the lungs and release pulmonary leukotrienes. In the lungs there is also upregulation of proinflammatory cytokines, substance-P, TNF-α, IL-β, and IL-6.[28,29] These kinins are also demonstrated in the bronchiolar lavage within 24 hours

after acute TBI.[30,31] Substance-P and neurokinins have been shown to cause bronchoconstriction, increase in vascular permeability, mucosal edema, and pulmonary edema.

The vagus and the parasympathetic system have a protective anti-inflammatory role in the lungs. Vagus nerve stimulation inhibits release of proinflammatory cytokines, TNF-α, IL-1 IL-6, IL-8, and other inflammatory mediators. Medullary injury may initiate anti-parasympathetic activity adding to inflammatory response in the lung and exaggeration of ALI. Whatever may be the immune mechanism involved, brain injury produces ALI and ARDS. There is initial increase in airway resistance due to bronchoconstriction.[30,31] Mucosal and alveolar edema results in hypoxia. Loss of surfactant results in airway closure, alveolar collapse, and atelectasis. Ventilation–perfusion mismatch and shunt result in impaired oxygenation. PaO_2/FiO_2 ratio of < 300 is a good predictor of developing ARDS. The incidence of ARDS varies from 20 to 25% in isolated head injury and an independent predictor of mortality, poor neurological outcome, and is associated with longer ICU and hospital stay. Low GCS, presence of mass lesion with midline shift in the first scan, induced hypertension, need for vasopressors, young patients, presence of associated comorbidities such as hypertension, diabetes, chronic obstructive pulmonary disease (COPD), sepsis, cardiovascular, and renal and hematological dysfunctions are factors likely to be associated with development of ARDS.[32,33] In addition, mechanical ventilation for ARDS with high tidal volume, high positive end-expiratory pressure (PEEP), recruitment maneuvers, and permissive hyperpnea itself may aggravate ARDS.[34] Inadequate and improper ventilation strategies may result in aggravation of inflammation that could extend to other systemic organs. Most ARDS patients die of multiorgan failure and not of pulmonary dysfunction.[35,36] ALI worsens the neurological outcome in patients with TBI.[37] ARDS can lead to hippocampal injury, resulting in memory deficits and cognitive dysfunction.[38]

Pneumonia

Pneumonia generally presents around 5 to 7 days after TBI. The incidence of pneumonia varies between 45 and 70%[3,4] The nosocomial infection is the most common cause of pneumonia in head injury. Altered sensorium and obtunded pharyngeal and laryngeal reflexes predispose to aspiration. Older patients with diabetes, obesity, chronic pulmonary diseases, and more specifically use of barbiturate coma have been associated with development of pneumonia.[39] Intubated patients on mechanical ventilation increase the risk of ventilator-associated pneumonia (VAP). Microaspiration, sedation, use of muscle relaxants, airway colonization, altered natural barrier due to the presence of endotracheal tube, and prior antibiotic usage increase the risk of VAP. Early initiation of oral or enteral feed and good oral care may reduce the risk of VAP.[40] Blood transfusion and immune suppression due to brain injury further promote infection. *Staphylococcus* is the most common organism to cause pneumonia in ICU in these patients, though superadded gram-negative infection can complicate pneumonia. Fever, purulent secretions, and presence of infiltrates in the chest X-ray suggest VAP. However, this should be differentiated from ALI, atelectasis, pulmonary contusion, pleural effusions, and pulmonary edema.

Cardiovascular Complications

Cardiovascular complications after severe head injury are common and often not attributed to TBI. The incidence varies from 45 to 65%.[4-7] The various complications include (1) hypotension, (2) hypertension, (3) arrhythmias, (4) shock, and (5) neurogenic stunned myocardium.

The pathogenesis of cardiac injury is related to the sympathetic storm associated with TBI, due to central neuroendocrine axis, activation of adrenal gland stimulation, and release of massive amount of catecholamines. Increased ICP also causes sympathetic response. Autonomic dysfunction has been reported in TBI patients with damage to the insula and hypothalamus.[41] This initiates complex and intense inflammatory response causing adverse reactions on the heart.[41-44] Increased ICP also releases catecholamine in the sympathetic nerve endings of myocardium causing myocytic injury and cardiac dysfunction. Interestingly, there is no correlation between systemic catecholamine levels and the degree of myocardial injury, which, however, is directly related to the degree of catecholamine release at the sympathetic endings of heart. This increase in sympathetic activity results in opening of β-1 controlled calcium channels and depletion of ATP resulting in myocardial injury, which may be exaggerated by reperfusion.[45,46] Myocardial injury results in mitochondrial dysfunction resulting in contraction-band-necrosis (CBN) characterized by focal myocytolysis and myofibrillar degeneration. These changes are more severe toward endocardium and progressively decrease toward epicardium. The severity of myocardial dysfunction is directly related to the degree of CBN, which in turn depends on the severity of TBI.[47] The neuroinflammatory response to TBI resulting in myocytolysis and CBN has been implicated in the pathogenesis of cardiac arrhythmias and myocardial dysfunction. Perfusion scans have shown that in addition to myocardial injury, catecholamines also produce vascular spasm of myocardial blood vessels resulting in regional perfusion abnormalities and ischemia. The clinical manifestations present in the form of hypotension and cardiac arrhythmias, ventricular dysfunction, and ischemic electrocardiogram (ECG) changes. Echocardiography may show regional wall motion abnormalities and systolic and diastolic dysfunction.[48,49] This cardiac dysfunction after neurogenic injury is often referred to as "neurogenic stunned myocardium or stress cardiomyopathy" (Takotsubo's cardiomyopathy or broken heart syndrome)[42-44] (►**Fig. 4**).

The sympathetic response (and dysfunction of parasympathetic system) may continue for 48 to 72 hours. During this period, tachycardia, hypertension, and hyperdynamic status may occur. Frequently, bradycardia and hypertension due to Cushing's response may occur. Even though hypertension may improve cerebral perfusion, severe hypertension may cause heart failure. β-Blockers have shown to be useful in controlling the hypertension and improve the outcome.[50]

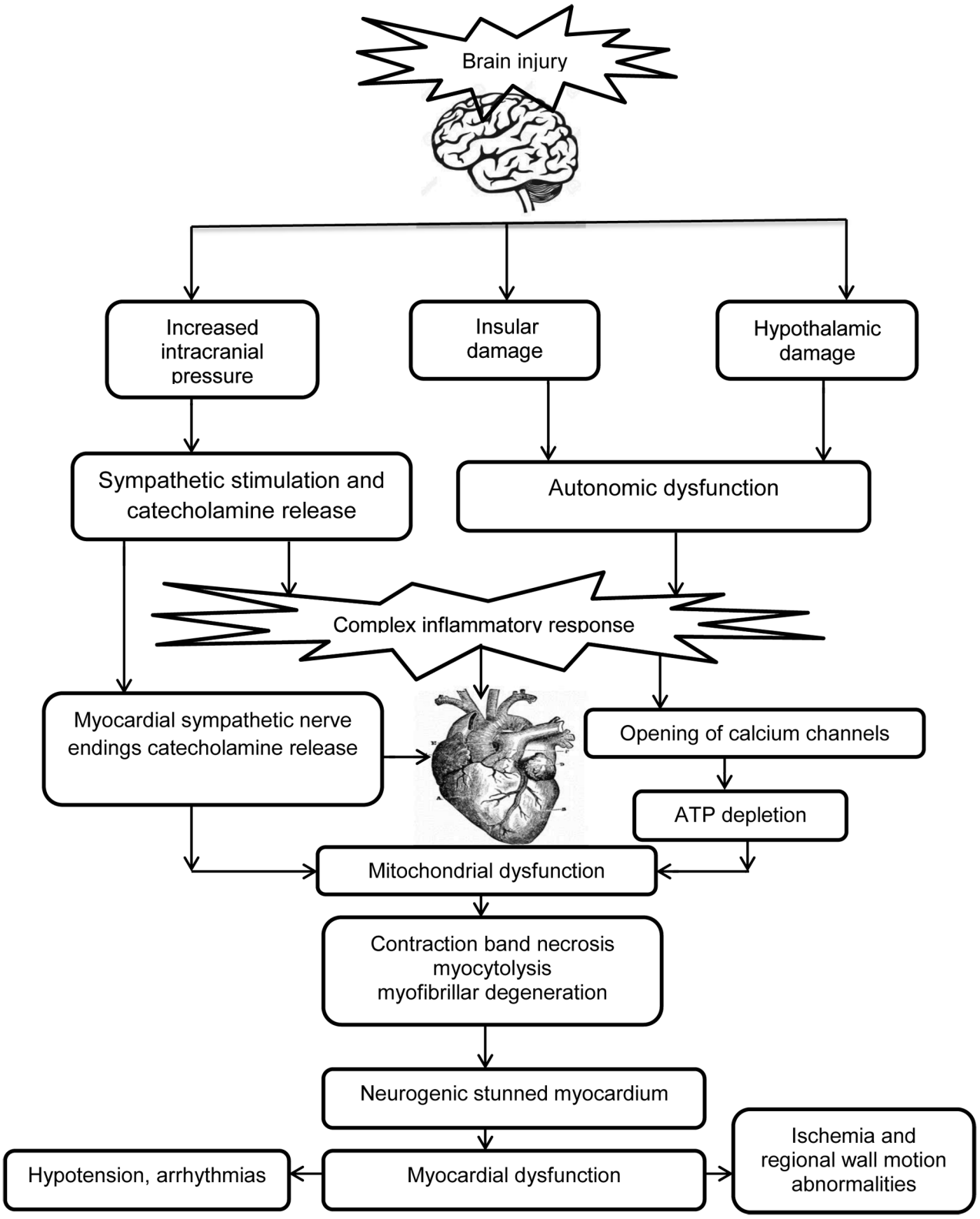

Fig. 4 Neurogenic stunned myocardium or stress cardiomyopathy (Takotsubo's cardiomyopathy or broken heart syndrome).

Once the surge of sympathetic stimulation decreases, the patient may develop hypotension. Hypotension in the immediate period of TBI is invariably due to extracranial causes such as hemorrhage or bleeding outside the cranium. However, hypotension not due to extracranial causes is invariably related to neurogenic hypotension, due to disruption of brainstem autonomic pathway, either due to direct injury or diffuse axonal injury, cerebral edema, medullary herniation, and spinal cord injury. Outcome in such cases is not favorable as compared with hypotension due to hemorrhagic shock, which, if treated with adequate blood transfusion, has better outcome.

ECG changes reflect the changes due to neurogenic stunned myocardium.[42] Most common changes are due to marked repolarization abnormality with QT prolongation and ST depression and T-wave changes occurring in 50 to 100% of patients. There could be bouts of polymorphic ventricular tachycardia, premature ventricular contractions, and wide QRS complexes. ECG changes may mimic acute coronary ischemia and may be difficult to differentiate from the myocardial infarction. Neurogenic ECG changes are generally asymptomatic. Cardiac enzymes changes may help in identifying ischemic or infarct events.[20,42,43] Repolarization changes revert with improvement in the neurological status. Sudden cardiac arrest has been noted to occur in patients with prolonged QTc.

Cardiac arrhythmias are not very common, occurring in about 25% of patients. Tachycardia, premature atrial or ventricular contraction, or atrial fibrillation may occur. However, most neurogenic arrhythmias are benign and disappear with improvement in neurological condition. However, prolonged QTc, torsades de pointes, and ventricular fibrillation occasionally occur in patients with insular lesions and may be life threatening.

Coagulation Disorders

Acute traumatic coagulopathy (ATC) is a well-known entity after severe trauma or crush injuries. The incidence of ATC in head injury varies depending on the definition of what constitutes coagulopathy. Many authors have used different parameters to define ATC, such as international normalized ratio (INR), platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen level, disseminated intravascular coagulation (DIC) score, modified coagulopathy score, and α_2-plasmin inhibitor value.[51] In a meta-analysis by Epstein et al, depending on the definition, the incidence varies from 7 to 83%. However, pooled incidence was 35.2%. The mortality rate in ATC was 17 to 86% in different studies.[51]

The reason why ATC occurs in TBI is because the brain contains the highest concentration of tissue factor (TF) or tissue thromboplastin in the body. Hence, any injury to the brain releases TF into the circulation initiating coagulation cascade. The process of fibrin formation may deplete coagulation factors and platelets, resulting in hypercoagulable state. Fibrinolytic activity may also initiate diffuse intravascular coagulation (DIC). ATC can cause bleeding and intracerebral hematoma formation and carry very high mortality.[52,53]

Traumatic coagulopathy is the result of imbalance between pro- and anticoagulants. With brain tissue injury, there is liberation of TF, which initiates the coagulation cascade. With endothelial damage, platelets, and activated factors, thrombin is formed by extrinsic pathway. The thrombomodulin (TM) present in the damaged endothelium combines with thrombin to form a complex, after which no thrombin is available for cleavage of fibrinogen. This complex activates protein C that inhibits cofactors V and VIII inhibiting further thrombin formation.[54,55] When hypotension is present, injury to endothelium releases tissue plasminogen activator (tPA) that splits plasminogen and activates fibrinolysis. Activated protein C consumes plasminogen activator inhibitor (PAI-1) that leads to increased tPA activity and hyperfibrinolysis.[54,55]

Acute coagulopathy due to brain injury is associated with platelet dysfunction.[56] Severity of platelet dysfunction is related to severity of brain injury, even though the platelet count may not be reduced. Davis et al[56] evaluated the platelet function in patients with isolated head injury by thromboelastography with platelet mapping (TEG-PM). The study showed no correlation between platelet count and platelet dysfunction as analyzed by TEG-PM. Hence platelet count per se may not be a good indicator of coagulopathy. The exact mechanism of platelet dysfunction is not clear. However, platelet ADP receptor inhibition has been shown to directly correlate with the low GCS, severity of TBI, and mortality.[56]

Coagulation disorders cause not only bleeding, blood loss, and intra- and extracranial hemorrhages but also shock. Widespread coagulation cascade results in systemic inflammatory response and sepsis. Immunological reaction to blood transfusion might also add to the inflammatory response. Sepsis and septic shock may result in organ dysfunction and multiorgan failure.[53]

Risk Factors for Acute Traumatic Coagulopathy in Head Injury

In a study by Abdelmalik et al[52] on ATC in isolated head injury, highest incidence of ATC was noted on day 2, both with mild and severe head injuries. However, ATC persisted for greater number of days with severe TBI as compared with mild injury. Other factors that were associated with ATC were (1) hyperthermia temperature > 38.5°C, (2) hypothermia temperature < 35°C, (3) hypotension with systolic blood pressure < 90 mm Hg, (4) oxygen PO_2 < 60 mm Hg, (5) GCS < 8, and (6) lactate level > 4.0 mM/L. All patients had high INR and PT. There was higher incidence of intracerebral hemorrhages and hematoma formation, with subarachnoid hemorrhages and midline shift. The length of hospital stay, incidence of deep vein thrombosis (DVT), and mortality was higher in ATC patients. In those patients who got discharged, long-term functional outcomes in ATC patients were not encouraging and most patients had significant moderate to severe cognitive dysfunction.[52] As reported by Epstein et al in their meta-analysis,[51] mortality was highest in patients who developed ATC within first 24 hours. Increasing age, low GCS on admission, male patients, pupillary reflex abnormalities, and cerebral hypoperfusion in patients with ATC, were associated with poor outcome. In a large multicenter population-based trauma registry-based study, Wafaisade et al[57] analyzed adult patients with isolated blunt TBI with intracranial AIS ≥ 3 and extracranial AIS score < 3, for acute posttraumatic coagulopathy upon arrival at emergency room (ER). The incidence of acute coagulopathy in isolated TBI was 22.7%. Overall hospital mortality was 50% in patients with coagulopathy. GCS < 8, presence of hypotension at the scene or ER, fluid resuscitation volume of > 2 L, and age > 75 years were all independent factors of mortality. Other significant complications between ATC and non-ATC patients were single organ failure (60.7% vs. 38.7%), multiorgan failure (35.7%

vs. 19.4%), intubation-free days (11 ± 13 vs. 20 ± 12), hospital length of stay (15 ± 22 vs. 18 ± 20), discharge from hospital (31.8% vs. 62.3%), 24-hour mortality (26.1% vs. 4.4%), and overall hospital mortality (50.4% vs. 17.3%), thus suggesting that patients with ATC develop more complications resulting in mortality.

Endocrine Dysfunction

Endocrine dysfunction has been reported after moderate to severe head injury in the first week after injury.[10] The incidence of acute dysfunction of both anterior and posterior pituitary is about 4 to 8%. However, their presentation is often subclinical and may be missed clinically. These may present in the form of adrenal dysfunction, thyroid dysfunction, and antidiuretic hormone dysfunction. However, gonadotrophins and growth hormone abnormalities are also reported in recovery and late phase of head injury.[10] Pituitary hematoma due to basilar fracture of the skull, raised ICP, hypoxia, hypotension, and cytokine inflammatory mediators released with TBI has been found to be associated with endocrine dysfunction. Treatment with phenytoin and use of etomidate may also precipitate pituitary dysfunction.[10]

Late-onset endocrine dysfunction after TBI may present between 6 months and 5 years after recovery from TBI. This endocrine dysfunction occurs after moderate to severe head injury; however, it is not commonly recognized in the acute phase but becomes evident in the chronic stage beyond 6 months.[10] In a study by Yang et al,[58] endocrine dysfunction was noticed in 0.4%, as compared with 0.3% in non-TBI patients at 1-year follow-up, and the incidence increased to 2% over 5-year follow-up.

The common endocrine dysfunctions during early phase of TBI are (1) anterior and posterior pituitary dysfunction occurring in about 4 to 8%, (2) adrenal dysfunction, (3) thyroid dysfunction, and (4) antidiuretic hormone dysfunction. However, gonadotrophins and growth hormone abnormalities are also reported during recovery and in the late phase of head injury.[10] In a study by Yang et al,[58] in a follow-up of 31,389 patients with head injuries for 5 years, endocrine dysfunction was noticed in 0.4% as compared with 0.3% in non-TBI patients at 1-year follow-up, and the incidence increased to 2% over 5-year follow-up. Direct injury to the pituitary gland due to base of the skull fracture, disruption of the infundibulum, and interruption in blood supply due to damage to hypophyseal blood vessels may result in pituitary hemorrhage or infarction, and hypothalamic damage, and has been responsible for hypopituitarism.

Adrenal insufficiency in the early phase may present as hemodynamic instability with inability to maintain blood pressure, in spite of adequate blood volume due to low systemic vascular resistance. Other manifestations are poor response to vasopressors, hypoglycemia, and hyponatremia. Serum cortisol levels are found to be low and are diagnostic of hypoadrenalism. Acute hypoadrenalism has been found to be more common in patients on mechanical ventilation. Recurrent infections, hyponatremia, and hypotension are common in chronic phase.[10,58]

Hypothyroidism due to pituitary cause has been reported in 17 to 24% of patients on days 1 and 2, after TBI. The peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3) is impaired, and abnormal form of T3 known as reverse T3 (rT3) has been found to be elevated. rT3 is a biologically inactive metabolite of T_4 formed by selective de-iodination. This condition is known as "euthyroid sick syndrome" due to dysregulation of thyrotropic feedback control, wherein the levels of T_3 and/or T_4 are abnormal, but the thyroid gland does not appear to be dysfunctional.[59] Clinical features of hypothyroidism may not be obvious. Low levels of thyroid-stimulating hormone (TSH) (due to pituitary lesion) and absence of TSH-releasing factor may result in prolonged coma and poor outcome. Chronic phase may present with typical features of hypothyroidism with low TSH levels.

Endocrine dysfunction after TBI occurring during late phase may present with vague symptoms such as nonspecific weakness, memory loss, attention problems, and others. These patients need to be evaluated with serum cortisol level, thyroid hormone levels, and other investigations.

Electrolyte Disturbances

Electrolyte disturbances are more common and present from day 2 of TBI. Piek et al and others have shown that electrolyte disturbances occur in more than 59% of patients with TBI.[3-6,10] Hyponatremia is the most common abnormality reported. This is due to syndrome of inappropriate ADH secretion (SIADH) and cerebral salt-wasting syndrome (CSWS). Both these conditions cause hyponatremia. However, the distinction between these two syndromes should be recognized, as the treatment differs. SIADH occurs due to excess ADH release, resulting in excess water retention, hyponatremia, and decreased serum osmolarity due to dilution and elevated urine osmolarity due to excretion of sodium into the urine. The blood volume in mild cases may be normal, but in severe cases, it may show increase. Hence SIADH is treated with water restriction. CSWS syndrome occurs due to elevated natriuretic factor and results in decreased blood volume and hyponatremia. Treatment of CSWS is by volume replacement with sodium containing fluid.

Injury to the posterior pituitary gland or hypothalamus may result in ADH deficiency producing hypernatremia and diabetes insipidus (DI). The incidence of DI is about 14.7 to 25%.[60] Risk factors for DI are severe TBI with low GCS and cerebral edema. Mild DI may be treated with fluid replacement, but severe DI may require vasopressin. DI was found to be one of the independent risk factors for mortality. ADH secretion disturbances are generally transient and recover within few days. Other electrolyte disturbances such as potassium and magnesium changes are more related to treatment.

Other Systems

Gastrointestinal System

As in any stressful conditions, TBI can result in acute gastric ulcers (Cushing's ulcer). They are observed endoscopically within 24 hours after TBI and may cause significant

hematemesis. Injury to the diencephalon and brainstem has been shown to increase gastrin and gastric acid output. TBI increases intestinal TNF-α, interleukins, and intercellular adhesion molecules. These immune mediators disrupt the intestinal barrier and increase intestinal permeability and endotoxin absorption. Ileus may occur due to endotoxin absorption. Progesterone has been shown to reduce intestinal inflammation.[61]

Metabolism

TBI induces hypermetabolic state with increase in caloric requirement by more than two to three times. Changes in the amino acids have been correlated with ICP and cerebral oxygen consumption. Elevated plasma leucine and isoleucine amino acids were associated with increased ICP and increased cerebral metabolic rate of oxygen ($CMRO_2$). However, increased phenylalanine level was associated with decreased ICP and $CMRO_2$.[10,62] Feedings should be initiated within 72 years, and enteral feeding should be preferred as this would maintain gut integrity and decrease infection. Increased stress response leads to hyperglycemia that is associated with increased morbidity and mortality.[10]

Temperature Regulation

Patients with head injury may develop fever, which may be infectious or noninfectious. TBI is often associated with impairment of body temperature. Many studies have shown that the brain temperature tends to be higher than the core body temperature by nearly 1°C.[62] This "neurogenic fever" has been shown to occur in 4 to 37% of patients with diffuse axonal injury and also in patients with frontal lobe injury or with base of skull fractures.[63] This noninfectious fever has been attributed to injury to hypothalamic temperature-regulating center. Autopsy studies have shown incidence of hypothalamic injury in 42% of patients dying of severe brain injury.[64] Neurogenic fever may also occur due to posttraumatic changes in brain metabolism due to hyperglycolysis, increase in cerebral blood flow (CBF), and also due to inflammatory response in the brain with the release of interleukins, particularly within 24 to 48 hours. Presence of blood in cerebrospinal fluid (CSF) or intraventricular bleed may lead to fever. Hyperthermia releases free radicals and excitatory amino acids and causes skeletal muscle proteolysis. Hyperthermia increases cerebral metabolic rate and blood–brain barrier breakdown. Sacho et al have shown that brain temperature more than 38°C and less than 36.5°C is associated with higher mortality.[65] Spontaneous hypothermia may occur in patients exposed to low ICU temperature unless adequate measures are taken to warm the patient. Hypothermia decreases both cellular and humeral immunity and increases the risk of infection.[66] Fall in brain temperature as compared with body temperature is associated with poor prognosis. Hypothermia occurs when brain death occurs.

Conclusion

The neurogenic inflammatory response to TBI releases cascades of inflammatory materials that cross the disrupted blood–brain barrier, ultimately causing suppression of peripheral immunity. Though these inflammatory mediators are supposed to be responsible for reparative process of the organs, they can cause cellular apoptosis. The materials released by apoptotic cells result in cascade of inflammation, infection, and sepsis. Septic shock may result in acute multiorgan failure. Hence, even though head injury may present as an isolated injury, if severe enough to cause disruption of blood–brain barrier, it may result in systemic organ dysfunction.

Conflict of Interest

None declared.

Acknowledgments

I would like to acknowledge the assistance of Dr. Anita Pramod in correcting the manuscript. I would also like to acknowledge the support provided by the colleagues of the Department of Anesthesiology, Manipal Hospital, for preparation of this manuscript.

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