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Case Report

Diffuse Brain Injury-Review of Literature and Representative Case Reports

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Abstract

Review of Literature: Diffuse brain injury includes diffuse axonal injury (DAI), diffuse vascular injury, hypoxic-ischemic injury and brain swelling. Adams described three grades of DAI. Diffuse vascular injury is usually incompatible with life. Ischemic hypoxia results in hemispheric hypodensity. Cerebral hemispheric swelling has the highest mortality.

Administration of mannitol, hyperventilation for short duration and infusion of barbiturate are useful to control ICP. Decompressive craniectomy is recommended in patients with severe brain edema. Transgastric jejunal feeding and early tracheostomy are recommended in ventilated patients. Cognitive rehabilitation therapy (CRT) is the fundamental component of comprehensive rehabilitation.

Case Reports: The 28 year male with DAI grade 1 improved in 2 weeks. The 19 year male with DAI grade 3 needed prolonged ventilation, tracheostomy and jejunal feeding. He improved by 2 months. A 3 year old child with DAI grade 1 improved in 2 weeks.

A 15 year old boy had progressive multiple intracerebral haemorrhages, suggestive of vascular injury. Decompressive craniectomy was done. He improved by three months.

A 20 year male with polytrauma had hemispheric hypodensity due to hypoxic ischaemia. He died after 18 hours.

A 27 year male had severe diffuse brain swelling, for which decompressive craniectomy was done. He died after 23 hours.

Conclusions: The classification of diffuse brain injury into four types and the various grading systems based on imaging are useful for prognostication. Brainstem lesions delay recovery of consciousness. Absence of basal cisterns and positive midline shift are predictors of death. Hypoxic ischaemia and brain swelling have poor prognosis.

Keywords

Diffuse axonal injury; Diffuse vascular injury; Hypoxic-ischemic injury; Diffuse brain swelling; Decompressive craniectomy, Cognitive rehabilitation therapy

Introduction

Severe Traumatic Brain Injury is a socioeconomic problem with mortality rate up to 40% and the disability rate of 55-77% [1]. Head injury can be classified into focal and diffuse. Focal brain damage includes subdural and epidural haematomas and intraparenchymal haematomas. Studies of Gennarelli et al. helped in the understanding of diffuse brain injury. Diffuse brain injury can be classified into diffuse axonal injury (DAI), diffuse vascular injury, hypoxic-ischemic injury and brain swelling [1]. DAI is common and comprise 40% to 50% of hospital admissions due to TBI. Rapid acceleration and deceleration of the head, as in high speed motor vehicle accidents, is the main mechanism of injury responsible for diffuse injury. Because of heterogeneity of brain structures, certain segments move at a slower rate than others, causing shear strain within the brain tissue [1]. Axons and small blood vessels are at risk for shear injury, due to their threadlike structure [2].

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Review of literature

Search was done in PubMed for literature about diffuse brain injury. Articles containing the classification of diffuse brain injury, relevant pathophysiology, clinical and imaging features of each type, and current concepts of treatment and future of management were reviewed. Importance was given to the four types of injuries and to the prognostication based on imaging. Brain Trauma Foundation's guidelines were referred for the consensus on treatment. The research on pharmacotherapy and stem cells also was reviewed.

Relevant pathophysiology of TBI

Primary effects of TBI are shearing of axons; break down of plasmalemma and rupture of microvessels [3]. Secondary effects include: inflammatory responses, cellular stress and apoptotic cascades. Following cell injury, the neurons rapidly depolarize and activate voltage gated Ca^{2+} channels, thereby increasing intracellular Ca^{2+}. Intracellular Ca^{2+} prompts reactive oxygen species (ROS) accumulation.

The vascular effects of TBI include vasospasm, hemorrhage and Blood Brain Barrier disruption. A potent vasoconstrictor, endothelin-1, is released from damaged pericytes. Brain edema can limit brain oxygen delivery and increase intracranial pressure. Ischemic hypoxia can cause the toxic release of hypoxia-inducible factor 1-alpha, leading to formation of Reactive Oxygen Species.

ROS can eventually contribute to disruption of the Blood Brain Barrier, edema, and neuroinflammation. Endoplasmic Reticulum Stress triggers the unfolded protein response (UPR). When the ER becomes overwhelmed and struggles to re-fold the unfolded proteins, the UPR ensues. Apoptosis and neurodegeneration are the end-game consequence of prolonged ER stress and the UPR. Secondary injury cascades initiated by glutamate receptors and the disruption of Ca^{2+} homeostasis will activate calcium-dependent proteases and disrupt energy-dependent processes [3].

Diffuse axonal injury

Adams described three grades of DAI [4]. In grade 1 there is histological evidence of axonal injury in the white matter of the cerebral hemispheres, the corpus callosum, the brain stem and, less commonly, the cerebellum; in grade 2 there is also a focal lesion in the corpus callosum; and in grade 3 there is in addition a focal lesion

in the dorsolateral quadrant or quadrants of the rostral brain stem. Diffuse axonal injury is clinically defined by coma lasting 6 hours or more after trauma, excluding cases of swelling or ischemia [5]. The clinical feature is coma with normal or minimally abnormal CT.

Hemorrhagic punctate lesions of DAI are seen only in10% of CT scan [2]. MRI is more sensitive for the diffuse and minute pathology found in DAI. Gradient-echo imaging is superior to spin-echo imaging for the detection of microbleeds [6]. Susceptibility Weighted Imaging (SWI) is more sensitive to hemosiderin deposition. In patients with severe DAI and resultant cerebral edema, venous stasis in SWI is an ominous sign. It appears as dark areas of susceptibility artifacts outlining engorged veins [2]. Studies show a correlation between the time taken for recovery of consciousness and the degrees of brain injuries seen on MRI [7]. Patients with lesions on cerebral white matter and corpus callosum have a tendency to recover consciousness earlier than patients with lesions on brain stem.

Diffuse vascular injury

Diffuse vascular injury is usually incompatible with life [8]. Patients with DVI also show severe (Grade 2 or 3) diffuse axonal injury (DAI). Both lesions depend on the same mechanism. Massive hemorrhages and convergent-type multiple hemorrhages are associated with poor prognosis [9].

Posttraumatic hyperemia is associated with intracranial hypertension. Cerebral hyperemia results in gross impairment of metabolic vasoreactivity and pressure autoregulation [10] and can delay neurological recovery [11]. Trans Cranial Doppler can detect this.

Cerebral vasospasm following traumatic subarachnoid hemorrhage is characterized by an earlier onset and shorter duration than that of aneurysmal SAH [12]. The initial hemorrhagic insult account for the vasospasm following tSAH. Mechanical alteration of the cerebral blood vessels due to direct impact also accounts for the pathophysiology. One mechanism is the release of a potent vasoconstrictor, endothelin-1, from damaged pericytes [3]. The rate of cerebral infarction on CT scans among TBI patients with vasospasm is 17% [12]. TCD offers an easy method for bedside monitoring. Nimodipine decreases cerebral infarction and unfavorable clinical outcomes [12].

Hypoxic- ischaemic injury

Tissue hypoxia after TBI can occur in the absence of macrovascular ischemia [13]. Combined oxygen 15-labeled positron emission tomography ($^{15}O_2$ PET) and brain tissue oximetry have demonstrated increased oxygen diffusion gradients in hypoxic regions. Pathologic features of microvascular ischemia are microvascular collapse, perivascular edema and microthrombosis. US Traumatic Coma Data Bank showed that hypoxia and/or hypotension were identified in 45% of cases and were associated with significant increases in morbidity and mortality [14]. This is especially common in cases of polytrauma with hemodynamic instability. Ischemic hypoxia results in hemispheric hypodensity [3].

Diffuse cerebral swelling

Brain edema following TBI will increase intracranial pressure and limit oxygen delivery [3]. In severe brain edema the cisterns will be compressed or absent [15]. A decrease in Hounsfield units of brain suggests edema. Diffuse Cerebral swelling has the highest mortality rate [16]. In children with head injury bilateral diffuse cerebral swelling is common [17]. Cerebral blood flow and CT density studies suggest that this is due to cerebral hyperemia. Prognosis in these children is better if there are no second lesions in CT.

Prognostication by imaging

Marshall et al. introduced a classification of head injury based on the initial CT scan findings [18]. The term "diffuse head injury" is divided into four subgroups: Diffuse Injury I includes all diffuse head injuries where there is no visible pathology; Diffuse Injury II includes all diffuse injuries in which the cisterns are present, the midline shift is less than 5 mm, and/or there is no high- or mixed-density lesion of more than 25 cc; Diffuse Injury III includes diffuse injuries with swelling where the cisterns are compressed or absent and the midline shift is 0 to 5 mm with no high- or mixed-density lesion of more than 25 cc; and Diffuse Injury IV includes diffuse injuries with a midline shift of more than 5 mm and with no high- or mixed-density lesion of more than 25 cc. The mortality rate after diffuse injury I is 10%, while after grade IV is greater than 50%.

Maas et al. introduced Rotterdam scoring system by including following parameters with predictive value: status of basal cisterns, shift, traumatic subarachnoid or intraventricular hemorrhage, and presence of different types of mass lesions [19]. The two strongest predictors of early death are absence of basal cisterns and positive midline shift [20]. In severe head injury with irreversible brain damage, there will be diffuse hemispheric hypodensity on CT scan, with loss of gray- white differentiation and with relative increase in the density of the thalami, brainstem, and cerebellum [21]. It is known as the 'reversal sign' or 'white cerebellum sign'.

Firsching et al. classified severe head injury based on magnetic resonance imaging [22]. Grade I - lesions of the hemispheres only. Grade II - unilateral lesions of the brain stem at any level with or without supratentorial lesions. Grade III - bilateral lesions of the mesencephalon with or without supratentorial lesions. Grade IV - bilateral lesion of the pons with or without any of the lesions of lesser grades. Mortality showed significant rise from 14% in grade I lesions to 100% in grade IV lesions.

Abu Hamdeh et al. proposed Extended Anatomical Grading in Diffuse Axonal Injury using MRI. Stage I-hemispheric lesions; stage II-corpus callosum lesions; stage III-brainstem lesions; stage IV-substantia nigra or mesencephalic tegmentum lesions; all are subdivided by age (≥/<30 years) [23].

Treatment

If the patient is comatose (GCS score of 8 or less) the airway should be secured by endotracheal intubation [24]. Midazolam is used for sedation of patients with increased ICP since it reduces the cerebral blood flow and cerebral oxygen consumption. Propofol provides satisfactory sedation under controlled respiration and allows early neurological evaluation because of rapid emergence. Vecuronium is the preferred muscle relaxant because of short duration of action.

Mannitol at a dose of 0.25-1.0 g/kg is useful for the control of ICP. Hypertonic saline 3% is also used. Barbiturate therapy is effective for intractable intracranial hypertension. Thiopentone 2-10 mg/kg as a bolus, followed by continuous infusion of 1-6 mg/kg/hour, is recommended under EEG monitoring.

Hyperventilation lowers intracranial pressure (ICP) by the induction of cerebral vasoconstriction and subsequent decrease in cerebral blood volume [25]. But cerebral vasoconstriction may decrease cerebral blood flow to ischaemic levels. Current evidence favors

hyperventilation for short duration. $PaCO_2$ should be between 30-35 mm Hg.

Fourth Edition of the "Brain Trauma Foundation's Guidelines for the Management of Severe Traumatic Brain Injury" recommends ' a large frontotemporoparietal Decompressive craniectomy (not less than 12 × 15 cm or 15 cm diameter) over a small frontotemporoparietal DC for reduced mortality and improved neurologic outcomes in patients with severe TBI' [26]. Transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia. Early tracheostomy can reduce mechanical ventilation days.

Drugs for posttraumatic cognitive impairment are N-methyl-D-aspartate receptor (NMDA) antagonists or augmenters of catecholaminergic or acetylcholinergic function [27]. Amantadine, NMDA receptor antagonist, improves arousal. Methylphenidate augments cerebral levels of dopamine and norephinephrine and improves arousal, attention and processing speed. Bromocriptine acts directly on dopamine type 2 (D2) receptors and improves executive function. Donepezil, a centrally-selective acetylcholinesterase inhibitor, improves attention and memory. Citicholine activates the biosynthesis of structural phospholipids in neuronal membranes and enhances activity of dopamine, norepinephrine and acetylcholine. It can improve cognitive, motor, and psychiatric disturbances. Modafinil is approved by United States Food and Drug Administration (FDA) as wakefulness-promoting agent [28]. It has direct effect on synaptic levels of norepinephrine (NE) and dopamine (DA).

Brain injury results in changes in the existing connections and in the activity of neurotransmitters [29]. This reduces the effectiveness of specific constitutive actions. The spontaneous creation of new connections and strengthening of the newly created connections are involved in the phenomenon of brain plasticity. The fundamental component of comprehensive rehabilitation is cognitive rehabilitation therapy (CRT). Rehabilitation can be either by reconstruction or compensation of the lost functions. The neuropsychological rehabilitation emphasizes on training of attention and memory, visual perception, auditory or audio-visual stimuli, executive functions, communication, training in day-to-day abilities, strengthening self-evaluation and emotional therapy.

Future research

Neurogenesis in adult brain occurs in the subgranular zone in the dentate gyrus (DG) of the hippocampus and subventricular zone [30]. Neuronal and vascular regeneration play a role in brain recovery after brain injury. Thymosin beta 4 and S100B are stimulators for neurogenesis in animal models. Nitric oxide enhances neurogenesis and angiogenesis.

Preclinical studies utilizing stem cells have shown beneficial effects. Mesenchymal stem cells (MSC) release growth factors such as Fibroblast growth factor 2 (FGF-2), Vascular endothelial growth factor (VEGF), Brain-derived neurotrophic factor (BDNF). These growth factors enhance neurogenesis, angiogenesis, and synaptogenesis. Neural stem cells (NSCs)/NPCs reside in the ependymal lining, subventricular zone and hippocampus. NSC can be transplanted by stereotactic injection into the brain. Another type of stem cells studied is embryonic stem cell (ESCs).

Case Reports

Cases were selected to represent the types and grades of diffuse brain injury. Clinical features, imaging findings, course and outcome were analysed retrospectively. Patients with DAI grade 1 had good prognosis. The course of patients with DAI grade 3 and DVI was similar. Hypoxic ischaemic injury and diffuse brain swelling carried bad prognosis.

Patient 1- DAI grade 1

A 28 year male was brought in unconscious state after two wheeler accident. GCS was E1M3V1. Pupils were reacting. He was intubated and ventilated. CT brain showed subarachnoid hemorrhage. CT chest showed hemorrhagic contusions of lung. He was given fosphenytoin, nimodipine, cefpirome, methylprednisolone etc. ABG on ventilator was –Ph 7.42, PaO_2 - 166 mmHg and $PaCO_2$ - 30 mmHg. GCS on second day was E2 M5. MRI Brain was done. SWI sequence showed multiple microhaemorrhages in cerebral hemispheres (Figure 1) suggestive of DAI grade 1. On fourth day GCS was E3M5 and he was weaned from ventilator and extubated. Supplemental oxygen, Citicholine and multivitamins were given. CRT was given using audio-visual stimuli in an enriched environment. On 9th day he became conscious E4M6V4. He had memory impairment of the accident and of the incidents during last six months. Visual stimuli were given as albums on laptop. Slowly memory improved except that of the accident.

Patient 2- DAI grade 3

A 19 year male was brought unconscious after two wheeler accident. His GCS was E1M3V1. Right pupil reacted to light. Left pupil was of size 3 mm and nonreactive to light. CT brain showed multiple small haemorrhagic contusions in bilateral temporal regions, corpus callosum and midbrain, subarachnoid hemorrhage and effacements of sulcal spaces and cisterns (Figure 2), suggestive of DAI grade 3. He was ventilated. Gave mannitol, fosphenytoin, nimodipine, propofol, cefpirome etc. Jejunal feeding was given. MRI FLAIR showed the small contusions with more clarity (Figure 3). He remained E1M3 for 10 days. He had decorticated posturing. Opened eyes to call (E3) on 11th day. But motor response was M3 only. Tracheostomy was done. Motor response improved to M4 on 20th day and was weaned from ventilator. He obeyed commands (M6) after 6 weeks. Decannulation of tracheostomy tube was done at 2 months. Feeding tube was removed 2 weeks later. His cognition improved. He can read, speak and understand matters. But he has residual unsteady gait.

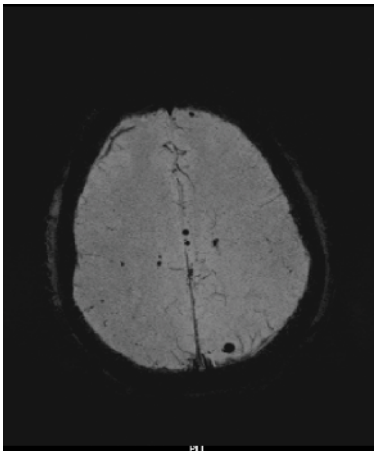

Figure 1: MRI SWI sequence showing multiple microhaemorrhages in cerebral hemispheres, suggestive of DAI grade 1.

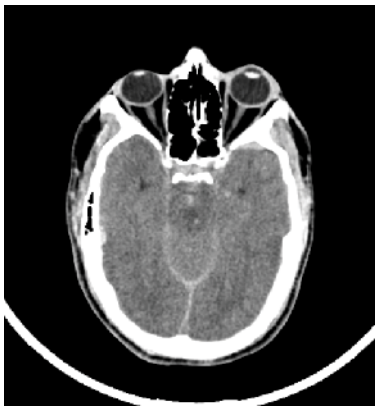

Figure 2: CT brain showing multiple small haemorrhagic contusions in bilateral temporal regions, corpus callosum and midbrain, subarachnoid hemorrhage and effacements of sulcal spaces and cisterns, suggestive of DAI grade 3.

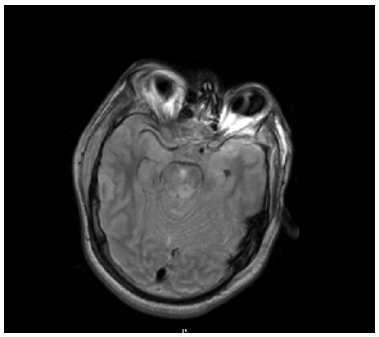

Figure 3: MRI FLAIR showing midbrain contusions.

Patient 3- Paediatric DAI

A 3 year old female child was brought unconscious after two wheeler accident. GCS was E1M2V1. Pupils were reacting bilaterally. She had continuous seizure. Chest auscultation revealed wheezes. She was given lorazepam, fosphenytoin, ceftriaxone, ondansetron etc. Intubation and ventilation was done. CT brain showed subarachnoid haemorrhage and multiple cerebral microbleeds (Figure 4). She was ventilated in SIMV mode. MRI FLAIR showed multiple small cerebral hyperintensities, suggestive of DAI grade 1 (Figure 5). On third day, she had E2M5 response and was weaned from ventilator. On fourth day she was extubated. On 7th day she had E4M5V2 response. Enriched environment was provided with sibling and parents. She gained near normal cognition in 2 weeks. She had late posttraumatic epilepsy. She is on treatment with phenytoin and valproate.

Patient 4- diffuse vascular injury

A 15 year old boy had an accident while travelling in bike. He became unconscious. BP was 190/110 mmHg. Pupils were reacting. GCS was E1M3V1. CT brain showed multiple small intracerebral haemorrhages (Figure 6). He was intubated and ventilated. Gave fosphenytoin, vitamin K, cefpirome, Fresh Frozen Plasma etc. Follow up CT brain after 2 hours showed increase in left cerebral hemorrhages with edema and midline shift, suggestive of vascular injury. There was no movement right side. Hyperosmolar therapy and thiopentone infusion were initiated. Emergency decompressive craniectomy was done using total intravenous anesthesia. Brain was congested and edematous. Duraplasty was done with durapatch. Follow up CT brain

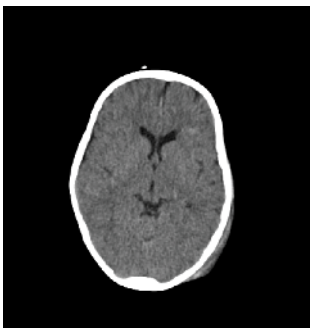

Figure 4: CT brain showing subarachnoid haemorrhage and multiple cerebral microbleeds.

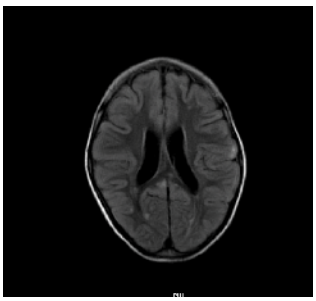

Figure 5: MRI FLAIR showing multiple small cerebral hyperintensities, suggestive of DAI grade 1.

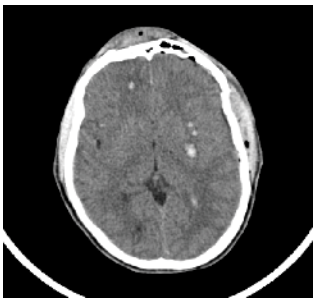

Figure 6: CT brain showing multiple small intracerebral haemorrhages.

showed decrease in mass effect (Figure 7). CT abdomen showed splenic laceration and splenectomy was done by surgeon. Nasojejunal tube was inserted and feed was given. Tracheostomy was done on 14th day. He had E2 M3 response after 20 days. Response improved to E4M5 after 5 weeks and he was weaned from ventilator. He was given audiovisual stimuli as music and laptop albums. After two months the edema resolved fully and the flap began to sink. Tracheostomy was removed successfully. Cranioplasty was done after 3 months. His memory and speech improved dramatically after going home. He has only residual right upper limb weakness.

Patient 5- hypoxic ischaemic injury

A 20 year male had bike accident and was brought in state of cardiac arrest. He was resuscitated, intubated and ventilated. GCS was E1M1V1. BP 80/60 mmHg. Pupils were nonreactive and dilated to 4 mm. He had nasal, oral and ear bleeding and fracture of shaft of left femur. CT Brain showed anterior skull base fractures and subarachnoid hemorrhage (Figure 8). Both hemispheres were hypodense and devoid of gray-white matter differentiation suggestive

of severe hypoxic ischaemic injury (Figure 9). He was given supportive care with nooradrenaline, packed red cells, fresh frozen plasma, crystalloids and colloids. He had cardiac arrest at 18 hours and succumbed to death.

Patient 6- Diffuse Brain Swelling

A 27 year male had two wheeler accidents and became unconscious. E1M1V1. Pupils were of size 2-3 mm and very sluggishly reacting to light. He had oronasal bleeding. He was intubated and ventilated. CT brain showed anterior skull base fractures, subarachnoid haemorrhage, absent cisterns, compressed ventricles and diffuse cerebral edema (Figures 10 and 11). He was given mannitol, nimodipine, fosphenytoin, levetiracetam and meropenem . Emergency bilateral frontotemporoparietal decompressive craniectomy was done. Brain was congested and tense bilaterally (Figure 12). Duraplasty was done. Ventilation was continued. Brain tension increased further and became hard as felt through the overlying flap. He had cardiac arrest at 23 hours and died.

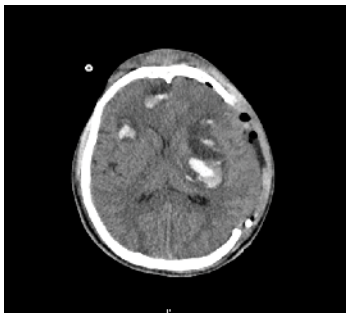

Figure 7: CT after decompressive craniectomy for left cerebral haemorrhages.

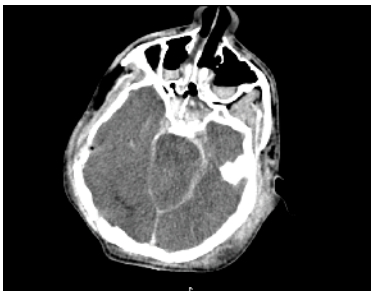

Figure 8: CT Brain showing anterior skull base fractures and subarachnoid hemorrhage.

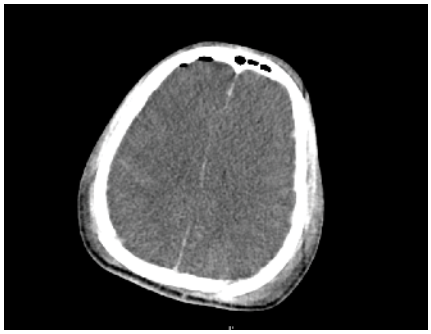

Figure 9: Hemispheric hypodensity and loss of gray-white matter differentiation suggestive of severe hypoxic ischaemic injury

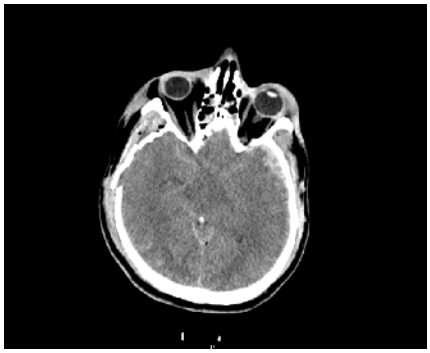

Figure 10: CT brain showing anterior skull base fractures, subarachnoid haemorrhage and absent cisterns.

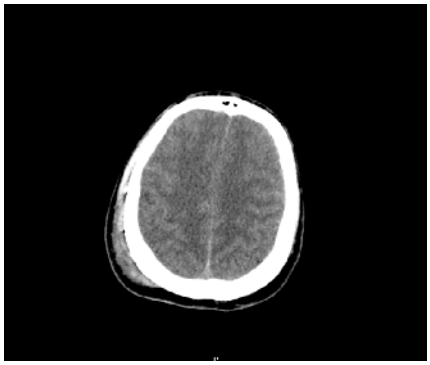

Figure 11: CT showing diffuse cerebral edema.

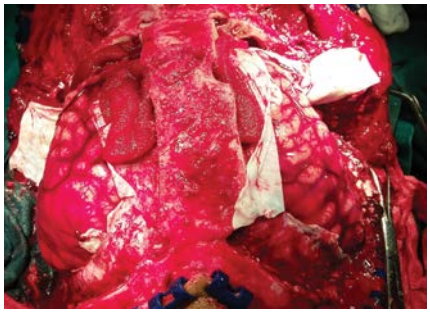

Figure 12: Bilateral frontotemporoparietal decompressive craniectomy showing congested and tense brain.

Discussion

Rapid acceleration–deceleration of the head causes diffuse brain injury. The classification of diffuse brain injury into four types is useful for the understanding of pathophysiology and prognostication and treatment. DAI is treated conservatively. MRI will delineate the minute lesions more clearly. SWI and FLAIR sequences are very useful. Brainstem lesions delay recovery of consciousness. Ventilation may be needed. Higher grade requires prolonged treatment.

Raised intracranial pressure requires stepwise treatment. Mannitol and hypertonic saline can be used for hyperosmolar therapy. Short course hyperventilation will help. Barbiturate infusion is needed for uncontrolled intracranial hypertension. Progressive diffuse vascular injury and diffuse brain swelling may require decompressive craniectomy.

Negative predictors indicate lesser chance of survival. Absence of basal cisterns and positive midline shift of more than 5 mm are indicators of brain edema and carries poor prognosis. Hypoxic ischaemic injury decreases chance of recovery. Hypodensity of hemispheres is a sign of irreversible brain damage.

Cognitive rehabilitation should be given for patients with functional impairments. Enriched environment and audio-visual stimuli should be given. Monoamine enhancer drugs can improve arousal and memory. Drug trials and stem cell research give hope for these patients. Stereotactic implantation of neural stem cells is under trial.

Conclusions

Diffuse brain injury includes diffuse axonal injury (DAI), diffuse vascular injury, hypoxic-ischemic injury and brain swelling. Adams described three grades of DAI. Diffuse vascular injury is usually incompatible with life. Ischemic hypoxia results in hemispheric hypodensity. Cerebral hemispheric swelling has the highest mortality.

Marshall et al., Maas et al. and Firsching et al. introduced different grading systems based on imaging. Patients with lesions on cerebral white matter and corpus callosum recover their consciousness earlier than patients with lesions on brain stem. The two predictors of early death are absence of basal cistern and positive midline shift.

Administration of mannitol, hyperventilation for short duration and infusion of barbiturate are useful to control ICP. Brain Trauma Foundation's Guidelines recommend large frontotemporoparietal Decompressive craniectomy for severe brain edema. Transgastric jejunal feeding and early tracheostomy are recommended in ventilated patients.

Drugs such as amantadine, methylphenidate, bromocriptine, donepezil, citicholine and modafinil are found to be useful for posttraumatic cognitive impairment, in trials. Cognitive rehabilitation therapy (CRT) is the fundamental component of comprehensive rehabilitation.

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