Introduction:

Brain injuries can be classified into mild, moderate, and severe categories (Saatman KE, et al. 2008). The Glasgow Coma Scale (GCS), the most commonly used system for classifying Traumatic Brain Injury (TBI) severity, grades a person's level of consciousness on a scale of 3–15 based on verbal, motor, and eye-opening responses to stimuli (Marion, 1999). It is generally agreed that a TBI with a GCS of 13 or above is mild, 9–12 is moderate, and 8 or below is severe (Jennett B , 1998 and Valadka AB, 2004).Similar systems exist for young children (Jennett B, May 1998). However, the Glasgow outcome score (GOS) grading system has limited ability to predict outcomes: score 1 death, score 2 persistent vegetative, score 3 severe disability, score 4 moderate disability, score 5 good recovery (Mazaux and Masson, et al 1997). A current model developed uses all three criteria of GCS after resuscitation, duration of post-traumatic amnesia (PTA), and loss of consciousness (LOC). It also has been proposed to use changes that are visible on neuroimaging, such as swelling, focal lesions, or diffuse injury as method of classification (Maas AI, 2008). Grading scales also exist to classify the severity of mild TBI, commonly called concussion; these use duration of LOC, PTA, and other concussion symptoms (Hayden MG, et al 2007).

Prognosis worsens with the severity of injury (Rao V and Lyketsos C, 2000). Most TBIs are mild and do not cause permanent or long-term disability; however, all severity levels of TBI have the potential to cause significant, long-lasting disability (Brown AW, et al 2008). Most mild TBI is completely resolved within three weeks, and almost all people with mild TBI are able to live independently and return to the jobs they had before the injury, although a portion has mild cognitive and social impairments (Crooks CY, et al 2007). Over 90% of people with moderate TBI are able to live independently, although a portion requires assistance in areas such as physical abilities, employment, and financial managing (Crooks CY, et al 2007). Most people with severe closed head injury either die or recover enough to live independently (Maas AI, et al 2008). Coma, as it is closely related to severity, is a strong predictor of poor outcome (Parikh S, et al 2007).

Prognosis differs depending on the severity and location of the lesion, type of trauma, time till the patient was transfered to specialized center and access to immediate, specialised acute management. Subarachnoid hemorrhage approximately doubles mortality (Armin SS, et al 2006). Subdural hematoma is associated with worse outcome and increased mortality, while people with epidural hematoma are expected to have a good

outcome if they receive surgery quickly (Zink BJ, 2001). Diffuse axonal injury may be associated with coma, and poor outcome (Maas AI, et al 2008). Following the acute stage, prognosis is strongly influenced by the patient's involvement in activity that promotes recovery, which for most patients require access to a specialised, intensive rehabilitation service.

Aim of the work:

The aim of this work is to define different factors affecting survival and outcome in patients with severe Traumatic Brain Injury (TBI).

Review of literature:

A-Introduction:

TBI is a leading cause of death and disability around the globe and presents a major worldwide social, economic, and health problem. It is the number one cause of coma, it plays the leading role in disability due to trauma, and is the leading cause of brain damage in children and young adults(Hannay HJ and Howieson DB, et al 2004).

In Europe it is responsible for more years of disability than any other cause (Maas AI and Stocchetti N, et al 2008).

It also plays a significant role in half of trauma deaths(Valadka AB, 2004).

Findings on the frequency of each level of severity vary based on the definitions and methods used in studies. A World Health Organization study estimated that between 70 and 90% of head injuries that receive treatment are mild, and a US study found that moderate and severe injuries each account for 10% of TBIs, with the rest mild(Narayan RK and Michel ME, et al 2002).

Epidemiology:

The incidence of TBI varies by age, gender, region and other factors. Findings of incidence and prevalence in epidemiological studies vary based on such factors as which grades of severity are included, whether deaths are included, whether the study is restricted to hospitalized people, and the study's location (Hannay HJ and Howieson DB, et al 2004).

The annual incidence of mild TBI is difficult to determine but may be 100–600 people per 100,000 (Park E and Bell JD, et al 2008).

In Egypt, Traumatic Brain Injury is an important cause of morbidity and mortality with an annual incidence higher than 2000 cases per 100000 population. The annual percentage of TBI is more than 2% of Egyptian population (Ehab Enab, et al 2011).

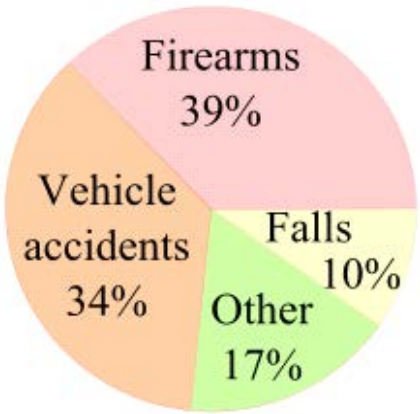


Figure (1): Causes of TBI fatalities in the US(León-Carrión J and Domínguez-Morales Mdel R, et al 2005).

B-Pathogenesis:

1) Aetiology:

The most common causes of Traumatic Brain Injury(TBI) in the U.S. include violence, transportation accidents, construction, and sports (Kushner D, 1998 andFaul, 2010).

Motor bikes are major causes, increasing in significance in developing countries as other causes reduce (Reilly P, 2007).

Firearmsand blast injuries from explosions are other causes of TBI, which is the leading cause of death and disability in war zones (Park E and Bell JD, et al 2008).

The estimates that between 1.6 and 3.8 million traumatic brain injuries each year are a result of sports and recreation activities in the US. In children aged two to four, falls are the most common cause of TBI, while in older children traffic accidents compete with falls for this position (Granacher , 2007).

TBI is the third most common injury to result from child abuse. Abuse causes 19% of cases of pediatric brain trauma, and the death rate is higher among these cases (Elovic E and Zafonte R, 2005).

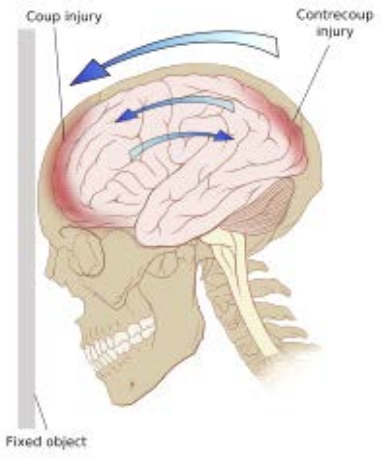
Etiology in children:

Most head injuries occursecondary to motor vehicle accidents, falls, assaults, recreational activities, and child abuse. The percentage of each contributing factor differs between studies, and the distribution varies according to age, group, and sex. A few factors (eg, seizure disorder, attention deficit disorder, and drug use) are known to enhance the vulnerability of the child or adolescent to this type of trauma. Infants and young children are

more vulnerable to abuse because of their dependency on adults and inability to defend themselves. Motor vehicle accidents account for 27-37% of all pediatric head injuries. In most cases involving children younger than 15 years, the victim is a pedestrian or a bicyclist; pedestrian accidents in children aged 5-9 years are the second most frequent cause of death. Young adults aged 15-19 years tend to be passengers in the accidents, and alcohol is often a contributing factor. Falls are the most common cause of injury in children younger than 4 years, contributing to 24% of all cases of head trauma. Recreational activities have a seasonal distribution, with peaks during spring and summer months. They represent 21% of all pediatric brain injuries, with the largest vulnerable group aged 10-14 years. Assault accounts for 10% of all pediatric brain injuries, and firearm-related injuries account for 2%. Child abuse has been identified as the cause of brain injury in 24% of pediatric patients younger than 2 years; it was suspected in another 32%. In children younger than 3 years, the severity of head injury can be successfully used to determine injury causes and mechanisms (Hymel KP and Stoiko MA, et al 2010).

2) Mechanism:

Physical forces



Figure(2):Mechanism of physical forces showing the coup injury and the contre-coup injury.

Ricochet of the brain within the skull may account for the coup-contrecoup phenomenon (Shaw NA, 2002).The type, direction, intensity, and duration of forces all contribute to the characteristics and severity TBI (Maas AI and Stocchetti N, et al 2008).

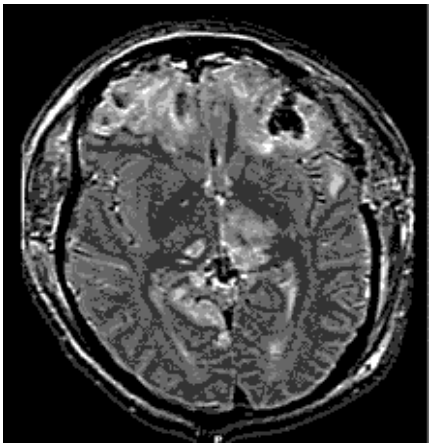
Forces that may contribute to TBI include angular,rotational, shear, andtranslational forces (Hardman JM and Manoukian A, 2002).

Even in the absence of an impact, significant acceleration or deceleration of the head can cause TBI; however in most cases a combination of impact and acceleration is probably to blame. Forces involving the head striking or being struck by something, termed contact or impact loading, are the cause of most focal injuries, and movement of the brain within the skull, termed noncontact or inertial loading, usually causes diffuse injuries (Saatman KE, 2008).

The violent shaking of an infant that causes shaken baby syndrome commonly manifests as diffuse injury. In impact loading, the force sends shock waves through the skull and brain, resulting in tissue damage.Shock waves caused by penetrating injuries can also destroy tissue along the path of a projectile, compounding the damage caused by the missile itself (Valadka AB, 2004).

Damage may occur directly under the site of impact, or it may occur on the side opposite the impact (coup and contrecoup injury, respectively) (Shaw NA, 2002).

When a moving object impacts the stationary head, coup injuries are typical, while contrecoup injuries are usually produced when the moving head strikes a stationary object (Morrison AL, 1998 and Poirier MP, 2003).



Figure(3): Male patient 50 years old ivolved in RTA with GCS 3, MRI of brain, axial image (flair) showing bi-frontal brain contusion after TBI (Morrison AL, 1998 and Poirier MP, 2003) .

A large percentage of the people killed by brain trauma do not die right away but rather days to weeks after the event; rather than improving after being hospitalized, some 40% of TBI patients deteriorate (Narayan RK and Michel ME, et al. 2002).

Primary brain injury (the damage that occurs at the moment of trauma when tissues and blood vessels are stretched, compressed, and torn) is not adequate to explain this deterioration; rather, it is caused by secondary injury, a complex set of cellular processes and biochemical cascades that occur in the minutes to days following the trauma. These secondary processes can dramatically worsen the damage caused by primary injury and account for the greatest number of TBI deaths occurring in hospitals (Xiong Y and Ghajar J, et al 2000).

Secondary injury events include damage to the blood–brain barrier, release of factors that cause inflammation, free radical overload, excessive release of the neurotransmitterglutamate (excitotoxicity), influx of calcium and sodium ions into neurons, and dysfunction of mitochondria. Injured axons in the brain's white matter may separate from their cell bodies as a result of secondary injury,potentially killing those neurons. Other factors in secondary injury are changes in the blood flow to the brain; ischemia (insufficient blood flow); cerebral hypoxia (insufficient oxygen in the brain); cerebral edema (swelling of the brain); and raised intracranial pressure (the pressure within the skull). Intracranial pressure may rise due to swelling or a mass effect from a lesion, such as a hemorrhage. As a result, cerebral perfusion pressure (the pressure of blood flow in the brain) is reduced; ischemia results. When the pressure within the skull rises too high, it can cause brain death or herniation. A particularly weak part of the skull that is vulnerable to damage causing extradural haematoma is the pterion, deep in which lies the middle meningeal artery which is easily damaged in fractures of the pterion. Since the pterion is so weak this type of injury can easily occur and can be secondary due to trauma to other parts of the skull where the impact forces spreads to the pterion (Ghajar J, 2000 and Morley EJ, 2008).

Altered autoregulation of cerebral blood flow:

Because the brain has minimal ability to store energy, it depends primarily on aerobic metabolism. The delivery of oxygen and metabolic substrate to the brain is maintained by a constant supply of blood, referred to as cerebral blood flow (CBF). CBF, defined as the amount of blood in transit through the brain at any given point in time, is estimated to be 50 mL/100 g/min in a healthy adult and is known to be much higher in children. However, the minimum amount necessary to prevent ischemic injury remains unknown. CBF is influenced by mean arterial blood pressure (MAP), ICP, blood viscosity, metabolic products, and brain vessel diameter. CBF should not be confused with cerebral blood volume (CBV), which represents the amount of blood present in the brain vasculature. Because brain tissue and CSF volumes remain relatively stable, acute changes in CBV are mostly responsible for acute changes in ICP. CBV depends primarily on the diameter of intracranial vessels, so therapeutic interventions to reduce intracranial blood vessel diameter (vasoconstriction) are the most effective methods to acutely reduce elevated ICP. Hyperventilation, in the acute phase, decreases ICP by decreasing CBV via alkalosis-induced cerebral vasoconstriction. The brain maintains constant blood flow through a mechanism known as autoregulation. This process occurs over a wide range of blood pressures through changes in cerebral resistance in response to fluctuations in MAP pressure. At a MAP of 60-150 mm Hg, CBF is maintained. At 60 mm Hg, the cerebral vasculature is maximally dilated. At 150 mm Hg, it is maximally constricted. (These are adult ranges; pediatric ranges are unknown but are likely age-dependent.) Fluctuations of MAP beyond either end of this range lead to alterations in CBF and contribute to ischemia or disruption of the blood-brain barrier. Several mechanisms are known to affect autoregulation of CBF; they may be divided into the following categories:

- Metabolic products
- Arterial blood gas content

- Myogenic factor
- Neurogenic factors
- Endothelium-dependent factors

The effects of these mechanisms are not fully known, and their mechanism of action is still under experimental investigation. CBF is closely linked to cerebral metabolism. Although the mechanism of coupling is not clearly defined, it is suspected to involve vasodilators released from neurons. Several factors have been implicated, such as adenosine and free radicals. Pathophysiologic states that are known to increase the metabolic activity (eg, fever and seizure activity) lead to an increase in CBF. CBF can be altered by changes in the partial pressure of oxygen or carbon dioxide. Alteration in the partial pressure of oxygen acts on the vascular smooth muscle through mechanisms that remain unclear. Hypoxia causes vasodilatation with significant increase in CBF. Increases in oxygen pressure result in dose-dependent vasoconstriction, although to a less pronounced degree than hypoxia-induced vasodilation. Hypercarbia increases CBF up to 350% of normal, while hypocapnia produces a decrease in blood flow. The mechanism appears to involve alteration in tissue pH that leads to changes in arteriolar diameter. This mechanism is preserved even when autoregulation is lost. However, renal compensation for respiratory alkalosis causes tissue pH levels to normalize, restoring CBF, which limits the effectiveness of prolonged hyperventilation for control of elevated ICP. The myogenic mechanism was long considered to be the most important in the autoregulation process. Changes in the actin-myosin complex were thought to lead to rapid changes in the vasculature diameter, thus affecting the CBF. It has now been shown that changes in the actin-myosin complex mostly cause dampening of arterial pulsation and have little direct effect on cerebral autoregulation. The neurogenic mechanism is represented by the effect of the sympathetic system on the cerebral vasculature. The sympathetic nervous system shifts autoregulation toward higher pressures, whereas sympathetic

blockade shifts it downward. Studies have identified nitric oxide (NO) as one of the factors affecting cerebral autoregulation; it does so by producing relaxation of cerebral vessels. NO is present in several conditions, such as ischemia, hypoxia, and stroke. It is generated by different cells at rest but also under direct stimulation by factors such as cytokines. Alterations in CBF during periods of hyperoxia, hypoxia, hypercarbia, and hypocarbia occur due to changes in local NO production. Vasodilation from somatosensory stimulation occurs through changes in neurogenic NO production, and impaired vasodilation associated with endothelial dysfunction appears to be due (at least in part) to the production of reactive oxygen species and reduced NO bioavailability (Toda N and Ayajiki K, et al 2009).

Traumatic brain injury (TBI) may lead to loss of autoregulation through alteration of any of these mechanisms. One study found that mild TBIs are more likely than orthopedic injuries to cause transient or persistent increases in postconcussive symptoms during the first year after injury. These mechanisms represent the foundation on which the medical management of increased ICP and cerebral perfusion pressure (CPP) is based in patients with traumatic brain injury (Yeates KO and Taylor HG, et al 2009).

3) Pathology:

Damage from TBI can be focal or diffuse, confined to specific areas or distributed in a more general manner, respectively. However, it is common for both types of injury to exist in a given case (Smith DH and Meaney DF, et al 2003).

Diffuse injury manifests with little apparent damage in neuroimaging studies, but lesions can be seen with microscopy techniques post-mortem, and in the early 2000s, researchers discovered that diffusion tensor imaging (DTI), a way of processing MRI images that shows white matter tracts, was an effective tool for displaying the extent of diffuse axonal injury. Types of injuries considered diffuse include edema (swelling) and

diffuse axonal injury, which is widespread damage to axons including white matter tracts and projections to the cortex (Kraus MF and Susmaras T, et al 2007).

Focal injuries often produce symptoms related to the functions of the damaged area. Research shows that the most common areas to have focal lesions in non-penetrating traumatic brain injury are the orbitofrontal cortex (the lower surface of the frontal lobes) and the anterior temporal lobes, areas that are involved in social behavior, emotion regulation, olfaction, and decision-making, hence the common social/emotional and judgment deficits following moderate-severe TBI. Symptoms such as hemiparesis or aphasia can also occur when less commonly affected areas such as motor or language areas are, respectively, damaged (Bayly PV, Cohen TS, et al 2005).

One type of focal injury, cerebral laceration, occurs when the tissue is cut or torn. Such tearing is common in orbitofrontal cortex in particular, because of bony protrusions on the interior skull ridge above the eyes. In a similar injury, cerebral contusion (bruising of brain tissue), blood is mixed among tissue. In contrast, intracranial hemorrhage involves bleeding that is not mixed with tissue(Valadka AB, 2004).

Hematomas, also focal lesions, are collections of blood in or around the brain that can result from hemorrhage (Parikh S and Koch M, et al 2007).

Intracerebral hemorrhage, with bleeding in the brain tissue itself, is an intra-axial lesion. Extra-axial lesions include epidural hematoma, subdural hematoma, subarachnoid hemorrhage, and intraventricular hemorrhage. Epidural hematoma involves bleeding into the area between the skull and the dura mater, the outermost of the three membranes surrounding the brain. In subdural hematoma, bleeding occurs between the dura and the arachnoid mater. Subarachnoid hemorrhage involves bleeding into the space between the arachnoid membrane and the pia mater. Intraventricular hemorrhage occurs when there is bleeding in the ventricles(Barkley JM and Morales D, et al 2006).