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Brain Grafting for the Repair of Traumatic Brain Injuries: A Future Prospective

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Abstract: *Traumatic brain injury is leading cause of morbidity and mortality in both developed and developing countries. Preliminary studies about the efficacy of cell therapy are presently being translated to clinical trials. Only few significant works has been focused on cell therapy applications for a wide range of diseases, including cardiac disease, bone disease, hepatic disease, and cancer. Traumatic brain injury is a devastating event for which existing therapies are limited. In this review the authors discuss the current status, background, epidemiology, pathophysiology, diagnosis and future prospective treatment of Traumatic Brain Injuries.*
Key words: *Brain Grafting, Neural Grafting, Pathophysiology, Traumatic Brain Injuries, Treatment*

I. Introduction

Traumatic brain injury (TBI) is leading cause of morbidity and death in both developed and developing countries. The frequency of TBI is high, and it is a crucial and vital problem for doctors and a considerable source of grief for patients. Presently no treatment exists to reinstate lost neurological function after any traumatic brain injuries. Typing or grafting of neuronal cells can be a useful method in treating individuals with TBI. However, Human stem cell transplantation trials are there and have now been undertaken for 6 indications: Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis, syringomyelia, and, spinal cord injury but it showed evident practical benefits in few patients of Parkinson's disease [1].

If transplantation is carried out into the injured brain and spinal cord, by the bone marrow-derived mesenchymal stromal cells (MSCs) than it may provide therapeutic benefit. To date, no randomized, controlled human clinical studies have been reported of the transplant of precursor cells for any kind off CNS injury. Clinical studies have been initiated in spinal cord injury with Schwann cells, human olfactory ensheathing glia and MSCs [2, 3]

This paper reviews the clinical condition of brain tissue injury and the various prospective including brain grafting which can be a promising treatment.

II. Background

Traumatic brain injury (TBI) is a non deteriorative, not inherited insult to the brain from an external mechanical force, possibly leading to perpetual or transitory impairment of cognitive, psychological, physical and socio-physiological functions, with an associated dwindled or altered state of consciousness. The definition of TBI has not been persistent and tends to inflect according to specialties and situations. Sometimes, the term brain injury is used commonly with head injury, which may not be related with neurological deficiency. The definition also has been problematic with alterations in inclusion criteria.

TBI still shows the leading cause of morbidity and death in individuals under the age of 45 year in the world [4].

It is referred as a "Silent Epidemic" because the complications from TBI, such as changes affecting sensation, thinking, language, or feelings, may not be readily evident or may not be obvious. In addition, awareness about TBI among the general public is limited.

TBI which is well-known as, head injury, acquired brain injury, or brain injury, causes substantial or considerable impairment and mortality. It takes place or happens when a sudden trauma injures the brain and disrupts normal brain function. The severity of TBI may range from "lenient" (a brief change in mental status or consciousness) to "Intense" (prolonged period of unconsciousness or loss of memory after the injury).

III. Biomechanical And Neuropathological Classification of TBI

The main principal mechanisms of TBI are classified as:

(a) Central brain damage due to contact injury types resulting in contusion, abrasion, laceration, and intracranial haemorrhage; or

(b) Diffuse brain damage due to acceleration/deceleration types of injury results in diffuse axonal injury or brain swelling. The result from head injury is determined by two considerable different mechanisms/stages:
(i) The primary damage (mechanical damage) emerging at the moment of impact. In treatment terms, these sorts of injuries are very sensitive to preventive but not in therapeutic measures.
(ii) The secondary delayed non-mechanistic damage shows consecutive pathological activities initiated at the moment of injury with delayed clinical presentations. Cerebral ischemia and intracranial hypertension refer to secondary damages, in treatment terms; these sorts of injuries are sensitive to therapeutic interventions [4].

IV. Epidemiology

Lack of Consistency in the clarification and classification of TBI, along with variations in data collection, has made it difficult to describe precisely. Problems with TBI data collection include the fact many sufferers or patients with Lenient/mild TBI may not be present to the hospital, and the ones who do present may be discharged at the emergency department (ED) without adequate documentation. The centre for disease control and prevention (CDC) (2007) estimates that 1.1 million ED visits, 235,000 hospitalization and 50,000 deaths occur as a result of TBI [5].

In United States of America approximately 1.7 million people undergoes a TBI annually, of which, 52,000 people die; 275,000 people get hospitalized; and 1,365,000 people, which is approximately 80%, who are treated and released from ED.TBI is a contributing factor to a third (30.5%) of all injury-related deaths in the United States [6,7].
The overall occurrence of TBI in the United States was roughly calculated to be around 538.2 for 100,000 populations, or around 1,500,000 new cases in 2003. Rather moderately lower rates are reported in Europe (235 per 100,000) and Australia (322 per 100,000) [7, 8].

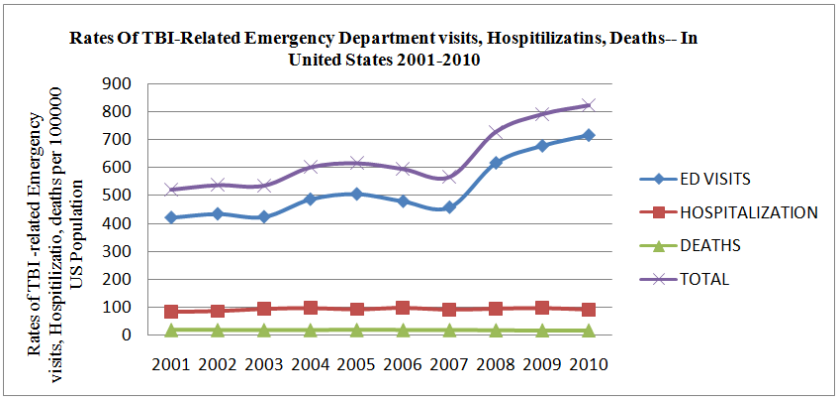

Fig. 1 Rates of TBI-related Emergency Department Visits, Hospitalizations, and Deaths — United States, 2001–2010

Table 1: Rates of TBI-related Emergency Department Visits, Hospitalizations, and Deaths — United States, 2001–2010 [8]

	ED Visits	**Hospitalizations**	**Deaths**	**Total**
2001	420.6	82.7	18.5	521.0
2002	433.9	85.6	18.3	537.2
2003	423.3	94.6	18.2	535.4
2004	486.3	97.6	18.1	601.3
2005	505.0	92.8	18.6	615.7
2006	478.9	98.7	18.2	595.1
2007	457.5	91.7	18.2	566.7
2008	616.4	95.5	17.7	728.9
2009	677.4	98.0	17.2	791.9
2010	715.7	91.7	17.1	823.7

Rates of TBI are found to be quite highest in the very young (age group zero to four years) and is common in adolescents as well as in young adults (15 to 35 years); As with most traumatic injuries, the incidence of TBI is notably higher in men in contrast to women, with ratios that range between3-4:1 (Male: Female) [6, 9].

V. Pathophysiology of TBI

The comprehension of the pathophysiology after TBI is a necessity for adequate, ample and patient-oriented treatment. The primary damage, which represents the direct mechanistic damage, cannot be influenced therapeutically. The primary harm or trauma to the head causes a rapid distortion of tissues present in the brain with destruction of brain parenchyma and blood vessels which causes damage to cell membranes with the prompt instantaneous release of intracellular contents [12, 13]. This initial injury cannot be treated, only prevented. The target of the treatment is the delaying of the secondary damage i.e., delaying in the non-mechanical damage. It is influenced by changes in cerebral blood flow (hypo perfusion and hyper perfusion), which leads to the impairment of cerebrovascular auto regulation cerebral metabolic dysfunction and inadequate cerebral oxygenation. Moreover, excitotoxic cell damage and inflammation may lead to apoptotic and necrotic cell death [4].

Primary injury in the brain, due to initial injury forces, causes tissue distortion and destruction in the early post injury period [14] .This initial injury cannot be treated, only prevented. Not all glial and neuronal damage occurs at the time of primary injury which is significantly aggravated by a complex cascade of neurochemical and pathophysiological events during the course of the initial hours and day [15].

As soon as the primary injury takes place, there are a colossal disturbances or disruption of the cellular ion homeostasis begin by excessive discharge/release of the excitatory amino acid neurotransmitters aspartate and glutamate which activates the glutamate receptors, a process known as excitotoxicity. The discharge/release of glutamate results in cellular influx of Na^+ and Ca^{2+} and efflux of K^+ [16, 17, 18, 19]. The influx of calcium ions is considered to be a key event of early post-TBI leading to damage the mitochondria, changes in gene expression, an increase in production of free radicals and also activation of calcium-dependent proteases including calpains, caspases and phospholipases resulting in extensive damage to the cytoskeleton [20, 21, 22]. The marked mitochondrial perturbation post-TBI [23, 24] leads to uncoupling of mitochondrial ATP synthesis at the time of supply of more or increased energy because of activation of energy-consuming ion transport systems and cell repair enzymes. Conversely, hyperglycolysis has been observed in various animal models and also in humans early following TBI [25, 26]. Unfortunately, the increased glucose demand and increase in local cerebral metabolic rate of glucose takes place at the time of reduced regional cerebral blood flow (rCBF) [27, 28, 29] and this uncoupling of blood flow-cerebral metabolism may be harmful to the injured brain post-TBI [30]. The increase in oxidative stress is one more vital characteristic of the post-injury process because the brain is highly sensitive to reactive oxygen/nitrogen species (ROS/RNS). Following TBI, there are several potential sources for overproduction of ROS/RNS, which includes the mitochondrial respiratory chain, oxidation of catecholamines, breakdown of membrane phospholipids, NADPH (in reduced form nicotinamide adenine dinucleotide phosphate) oxidase activation, increased in free iron which arises from breakdown of haemoglobin, infiltrating neutrophils and activation of nitric oxide synthetase occurring at a time when the intracellular and extracellular antioxidant defences are challenged and may become exhausted [31, 32]. Oxidative stress is presently assumed to play the major contribution to the secondary injury cascade following TBI by ROS/RNS influenced damage to cellular membranes and is organelles by lipid peroxidation, protein oxidation and nucleotide breakdown [33]

TBI induces a strong immune activation along with an acute inflammatory response with collapse of the blood–brain barrier (BBB), infiltration of peripheral immune cells, oedema formation, activation of resident microglia and astrocytes and also intrathecal release of cytokines [34, 35, 36]. A prominent up-regulation of several chemokine-related gene transcripts was recently observed following focal TBI in mice [22] and activated glial cells and leukocytes secrete a variety of neurotoxins including tumour necrosis factor(TNF) and the interleukin family of peptides [37, 38, 39]. Significantly, infiltrating the leukocytes which secretes myeloperoxidase may be an important source for ROS by producing hypochlorous acid [33].

TBI induced damage to the mitochondria initiates the of apoptotic cell death through an aperture of the permeability transition pore of mitochondria, the release and activation of pro-apoptotic factors including soluble cytochrome, apoptosis inducing factor and caspases [24, 40]. It should be emphasized that TBI causes not only apoptotic but also necrotic neuronal cell death [41]. Regardless of the mechanisms for cell death, widespread neuronal damage occurs and may be noticed even far from the site of injury, where the hippocampal region may be particularly sensitive [42].

In spite of the fact that, neuronal cell death has been given the predominating attention in the TBI field it is easily perceived or understood that traumatic axonal injury, frequently mention as diffuse axonal injury (DAI), is common following TBI. Significantly, DAI is a dominant contributor to the functional deficiency observed in TBI patients and is observed with high frequency in those hapless patients remaining in a persistent/tenacious vegetative state [43]. Axonal injury is categorized across injury severities and also in the TBI subtype [44]. Acute axonal disconnection at the time of impact is rarely or not often observed and only in patients with very severe TBI dying at the site of the accident. Instead, shearing and stretching of axons caused by the impact may occur in areas far from the place of impact and has been linked to the intra-axonal

cytoskeleton damage that ultimately leads to axonal failure and disconnection [45, 46]. Axonal swellings and axonal bulbs are the histological hallmarks of traumatic axonal injury, implying that axonal injury is an ongoing continuing process that may arise over hours to days [46]. It should also be highlighted that yet other factors, including disturbances in the neurotrophin, coagulation, endocrinological and neurotransmitter systems, may contribute to the pathology of TBI and be manipulated pharmacologically [47].

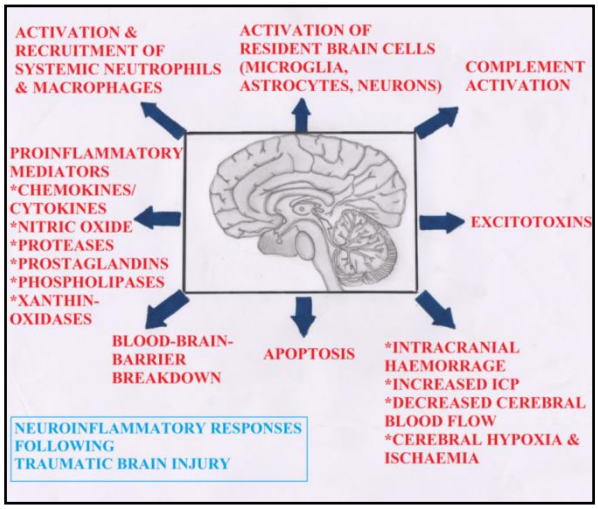

Fig 2. Simplified schematic of the complex neuroinflammatory response following traumatic brain injury.

VI. Diagnosis And Treatment of TBI

6.1 Diagnosis

In the past, roentgenograms were used to help diagnose skull fractures after head injury did not show much of any simultaneous or concurrent or contemporaneous intracranial lesions. These lesions were difficult to diagnose until the arrival of Computed Tomography (CT) scanning, which is presently the diagnostic imaging of choice in TBI cases [48, 49]. There are few different systems that are used by the doctors for the diagnosis of the symptoms of TBI. This section provides a brief discussion on the Glasgow Coma Scale (GCS) [9, 50, 51], Ranchos Los Amigos Scale (RLS) [51, 52] and Simplified Motor Score (SMS) [53].

6.1.1 Glasgow Coma Scale (GCS)

Table 2: Glasgow Coma Scale

Glasgow Coma Scale		
Eye opening (E)	Verbal Response (V)	Motor Response (M)
4 = Spontaneous 3 = To voice 2 = To pain 1= None	5 = Normal Conversation 4 = Disoriented conversation 3 = Words, but not coherent 2 = No words....only sounds 1 = None	6 = Normal 5 = Localizes to pain 4 = Withdraws to pain 3 = Decorticate posture 2 = Decerebrate 1 = None
		Total = E + V + M

The final score is given by adding the values of E+V+M

This number assists the doctors to categorize the possible/sensible degrees for survival, with a lower number indicating a more serious injury and a bad prognosis.

The Traumatic Coma Data Bank revealed that severe TBI is indicated when the GCS score is below 9 within 48 hours of the injury [54]. Glasgow Coma Scale scores of 13–15 characterize acute mild TBI, whereas lower Glasgow Coma Scale scores, 9–12 depute acute moderate TBI. Glasgow Coma Scale scores of 3–8 implies acute severe TBI [55].

6.1.2 Ranchos Los Amigos Scale (RLS)

The Ranchos Los Amigos Scale determines the levels of awareness, cognition, behaviour and interaction with the environment.

Table 3: Ranchos Los Amigos Scale

Ranchos Los Amigos Scale Levels		
Level	Response	Assistance needed
Level I	No response	Needs total assistance
Level II	Generalized response	Needs total assistance
Level III	Localized response	Needs total assistance
Level IV	Confused-agitated response	Needs maximal assistance
Level V	Confused-agitated response	Needs moderate assistance
Level VI	Automatic-appropriate response	Needs minimal assistance
Level VII	Purposeful-appropriate response	Needs Stand-by assistance

6.1.3 Simplified Motor Score (SMS)

The Simplified Motor Score (SMS) is a three-point scale which was developed to see and overcome the limitations of the GCS, such as its complexity and poor interrater reliability. The points are as given in the TABLE 4 [54]:

Table 4: Simplified Motor Score

Simplified Motor Score	
Obeys commands	2 points
Localizes pain	1 point
Withdraws to pain or worse	0 points

A study by Thompson et al. [53] determined that inside as well as outside of hospital setting, the SMS was similar to the GCS score for prediction of TBI outcomes [53].

6.2 Treatment

There is no successful treatment for TBI. It is not one disease. It has subtypes and some of them are: acute subdural haematoma (aSDH), neurocritical care (NCC); diffuse axonal injury (DAI); epidural haematoma (EDH).

6.3 Diagnostic and Therapeutic Approaches made in Treating TBI

6.3.1 Mesenchymal stromal cells (MSCs) which are derived from Bone marrow for the repair of various Central Nervous Systems (CNS) Injuries

In 2000 Chenet al., [56] first recorded the transplantation of MSCs for CNS repair after administration of bone marrow with a brain-derived neurotrophic factor (BDNF) into a model of middle cerebral artery occlusion (MCAo). Studies has been carried out for repair of CNS injury using Bone marrow derived MSCs with a prescriptive that the transplantation of bone marrow derived MSCs if introduced into the injured spinal cord or brain may provide therapeutic benefits/advantages. Many models of central nervous system (CNS) injury have been inspected, including that of ischemic stroke, TBI and traumatic injury of spinal cord in primate, rodent, and more recently, human trials. Several kinds of cells (precursor cells) have been transplanted into the injured CNS, including adult bone marrow-derived MSCs. No randomized, controlled human clinical studies have been reported of the transplantation of precursor cells for CNS injury till now. Clinical studies, however, have been carried out in spinal cord injury with human olfactory ensheathing glia, Schwann cells, fetal spinal cord and MSCs [2, 3]

Table 5: Potential mechanism of action of Transplanted adult bone marrow derives MSCs in CNS injury

(1) Transdiffertiation to replace neural cells, Neurons, Astrocytes, Oligodendrocytes.
(2) Neuroprotection Reduction of apoptosis. Reduction of inflammation. Reduction of demylination. Increased astrocyte survival.
(3) Creation of favourable environment Proliferation of endogenous neural progenitors. Proliferation of endogenous oligodendrocytes. Creation of cellular bridges and 'guiding strands'. Enhanced intercellular communication in astrocytes. Decreased thickness of glial scar. Production of fibronoctin to counteract glial scar.
(4) Expression of Growth factors or cytokines by MSCs or host environment BDNF NGF FGF2 VEGF TGF- β IGF 1

BNP SCF 1
(5) Vascular effects Restoration of blood flow. Repair of blood brain barrier. Reduction of oedema. Reduction of increased intracranial or intraspinal pressure. Angiogenesis.
(6) Remyelination by MSCs or Oligodendrocytes , Schwwann cells.
(7) Cell fusion.
Abbreviations: BDNF- Brain Derived Neurotrophic factor; BNP- Brain Natriuretic Peptide; CNS- Central Nervous System; FGF2- Fibroblast Growth Factor; IGF1- Insulin Growth Factor; MSC- Mesenchymal Stromal Cell; NGF- Nerve Growth Factor; SCF1- Stromal Cell Growth factor 1; VEGF- Vascular Endothelial Growth Factor.

However, several studies have shown remarkable functional improvement from transplantation of MSCs after either spinal cord injury or brain injury, the mechanisms are still not clear. TABLE 5 shows a list of potential beneficial mechanisms for transplanted MSCs in various CNS injuries, but it should be accounted that these are not mutually exclusive, and it is likely that several factors play a role.

There are controversies regarding the therapeutic efficiency or benefit of MSCs in CNS injury. Inconsistency in the data or literature may relate to differences in species(mice versus rat versus human), or even intraspecies variation [57]. It was reported that human MSCs shows significant donor dissimilarities after transplantation into the rat with injured spinal cord, with fluctuations in secretion patterns of cytokines and growth factors. Other differences may be due to the variety of injury models employed, culture conditions, methods of transplantation including number of cells injected, labelling methods and potential transfer to host cells. For human studies, it is also important to note the karyotype of the cultured cells, however to date; cytogenetic abnormalities among passaged human MSCs are admittedly infrequent or rare. Another point that remains to be address is the importance of cell dose in the transplanted inoculums and whether there is a safe upper limit.

6.3.2 Human stem cell transplantation trials

A stem cell transplant is also known as blood or marrow transplant - is the injection of healthy stem cells into the body to replace diseased or damaged stem cells.

Human stem cell transplantation studies have been undertaken for 5 indications:

Parkinson disease, Huntington disease, spinal cord injury, amyotrophic lateral sclerosis, and syringomyelia. Only for Parkinson disease, however, it has shown clear functional benefit for some patients. The determination of the target zone for neural progenitor cells (NPCs) transplantation for TBI is potentially more complex than for the above indications, due to the diverse injury responses and diffuse cell loss patterns, although up regulation of some neurotrophic factors in the injured host environment may favour the survival of transplanted NPCs. Transplantation of NPCs may be a potential treatment strategy for TBI due to their intrinsic advantages, including the secretion of neurotrophins. Neurotrophins having limited clinical applications but are critical for neuronal survival and repair [58].

VII. Future Prospective Treatment of TBI

Various kinds of organ transplants like transplant of the kidneys, liver, and even heart has received a significantly popular attention in recent years. Efforts to graft tissue in the central nervous systems of laboratory animals goes back at least to 1890 [59], although it was generally assumed that neurons in the CNS of mammals and humans could not regenerate or reproduce after injury and that, consequently, grafts of neuronal tissue were doomed to failure. Presently scientists become confident and hopeful about the possibilities of repairing damage in the CNS of mammals. Usually the researches were carried out with rats, but different other species, like mice and rabbits, have also been used for the experiments [60].

Various transplantation procedures have been tried in the effort for grafting of healthy neurological tissue to injure/damaged areas of the CNS [60]. The earliest approach was to insert the graft from one animal directly into a slit near the surface of another animal's cortex. As there was some success with this methodology in immature rats but it did not work as expected in mature animals. A more successful approach is to place the graft into a surgically prepared transplantation cavity. This procedure allows for a good control over the placement of the graft and the use of larger tissue pieces (usually from the brain matter of a rat embryo).

Anders Bjorklund and Ulf Stenevi, made a review of research on intracerebral neural implants in the year 1984 [61], which reports that the single most important factor for better survival of neural grafts is the developmental stage of the donor tissue and, to a lesser extent, the age of the recipient animal. In rats, studies show that there is no strong evidence of rejection of any neurological transplants by the body's immune system,

leading to the possibility that the brain may be an immunologically privileged site, partly because of its protective blood-brain barrier (BBB) [61].

Table 6. Early history of neuronal grafting in the mammalian Central Nervous System [62].

1890	W. G. Thompson	New York, USA	First attempt to graft adult CNS tissue to the brain.
1898	J. Forssman	Lund, Sweden	First report of neurotrophic effects of grafted tissue.
1907	G. Del Conte	Naples, Italy	First attempt to graft embryonic tissues to the brain.
1909	W. Ranson	Chicago, USA	First successful grafting of spinal ganglia to the brain.
1911	F. Tello	Madrid , Spain	First successful grafting of peripheral nerve to the brain.
1917	E. Dunn	Chicago, USA	First successful grafting of neonatal CNS to the brain.
1921	Y. Shirai	Tokyo, Japan	First demonstration of brain as an immunologically privileged site.
1924	G. Faldino	Pisa, Italy	First successful grafting of foetal CNS to the anterior eye chamber
1940	W. E. LeGros Clark	Oxford, UK	First successful grafting of foetal CNS to the neonatal brain.
1957	B. Flerko & J . Szentagothai	Pecs, Hungary	First successful intraventricular grafting of endocrine tissue.
1970 & 1971	Olson & Seiger, Das & Altman and Bjorklund & Stenevi		First reports for conditions of reliable transplantation to the brain and anterior eye chamber

Once the neurological transplants are successfully grafted into the damaged area, the implant stimulates and promotes a regenerative response already present in the recipient's brain as a result of the lesion. Research suggests that the transplant acts as a bridge to guide regenerating axons back to their original sites [60].

The Brain Cell transplantation therapy for Parkinson's disease holds great promise. A procedure for treating Parkinson's disease, in which chromaffin adrenal cells are transplanted into the caudate nucleus [63, 64]. Neural transplantation has emerged as a possible therapy for Parkinson's disease (PD). Clinical studies conducted during the 1990s, where dopaminergic neurons derived from the human embryonic brain were transplanted into striatum of patients with PD, provided proof-of-principle that long-lasting therapeutic benefits can be achieved. Subsequent studies, in particular two that followed a double-blind, sham surgery, placebo-control design, showed variable and mostly negative results. They also revealed that some patients develop involuntary movements, so called graft-induced dyskinesias, as side effects Thus, while nigral transplants clearly work well in select PD cases, the technique needs refinement before it can successfully be performed in a large series of patients [65].

Significant development has been made in the field of brain grafting over the last 15 years. Neurosurgeons have been involved directly in the preclinical and clinical efforts in this fascinating and promising field, along with their neuroscience colleagues. Through a better understanding of the complex mechanisms involved in response to transplants in the brain, new technologies and experimental strategies are being developed to improve the safety and efficacy of these procedures. The time is right for carrying out appropriate preclinical studies in rodents and nonhuman primates to answer one of the most basic questions: Is a tissue graft necessary for behaviour improvement in degenerative diseases such as PD, HD, AD or TBI? With available tools and technology and an open mind to new ideas, brain grafting has a tremendous potential in the neurosurgeon's armamentarium, both today and in the future [66].

If brain grafting is possible for TBI it will be a very promising treatment for the patients who are injured with TBI.

VIII. Conclusion

TBI, a dominant contributor to deaths and permanent disability worldwide, at present described as a progressive cell death process rather than an acute/sharp event [67].

In this review, we described the clinical conditions of brain tissue injury and the various prospective, but it should be noted that these are not mutually exclusive, and it is likely that several factors play a role Finally, we discuss future aspect offered by brain tissue typing as therapeutically approach for treating TBI.

Since no research data is available on brain tissue grafting on TBI, more investigation, and research is needed to understand the interaction between the transplanted cells and the host to optimize the chances of success before proceeding/going to the clinic. Cooperation between neurosurgeons, neurologists, and neuroscientists is required to translate cell transplantation therapy to the clinic in a timely but safe and effective manner. Further studies are required to determine the mechanisms underlying therapeutic benefits exerted by brain grafting in treating TBI in order to enhance its safety and efficacy in the clinic.

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