Review article

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Traumatic axonal injury in mild to moderate head injury - an illustrated review

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Abstract: Head injury forms the most common and serious form of trauma seen in India.Though data in India as a whole is sparse it does seem appropriate to say that mild to moderate head injury seems to form the major bulk of head injuries. Many such patients with normal CT scans who are discharged after a short period of ICU stay experience cognitive deficits, reduced attention spans and have problems with "executive functions" like planning, problem solving, abstract reasoning, judgment making etc. Some patients also have language deficits, problems with driving, hand eye coordination, behavioral changes and many other minor problems which may take a long time to recover. Most of these functional abnormalities are probably due to diffuse axonal injury.

Axonal injury is one of the common pathological entities in any severity of head injury and is a diagnosis of exclusion for almost all of the clinical symptoms which cannot be explained otherwise. A case has been illustrated in this regards.

The review throws light on the pathophysiology and some recent advances in imaging and treatment modalities of traumatic axonal injury due to mild to moderate head injury.

Keywords: axonal injury; mild to moderate head injury

INTRODUCTION

Diffuse brain injury may occur in the absence of impact forces, but is dependent on inertial forces that are commonly produced by motor vehicle crashes and, in some cases, falls and assaults and hence is sometimes also referred to as a "shear injury"[1-4]. In practice we define diffuse axonal injury as post-traumatic loss of consciousness which lasts for more than 6 hours in cases where no mass lesions were seen on routine imaging to explain the comatose state of the patient and more or less is a diagnosis of exclusion. However the term diffuse is probably a misnomer as the microscopic axonal pathology is more of a multifocal pattern of injury in the deep and subcortical white matter, more in the midline involving structures as the corpus callosum, splenium and the brainstem. In a large number of less severe forms of the pathology however there might not be any 'pick up of lesions' with most of the conventional forms of imaging.

The term axonal injury is also quite misleading as this term might mean anything from axonal disconnection (axotomy) to axolemmal swelling. Dr Sabina Strich in 1956 studied the postmortem specimen of five severely disabled individuals where she was able to microscopically demonstrate diffuse degeneration of the axons. She subsequently followed the above with 15 more cases of similar etiology and histopathological features postulating that it was immediate axonal shearing followed by cytoplasmic extrusion causing the finding, thus naming it diffuse degeneration as a result of angular acceleration of brain as a result of rapid head rotation[5,6].

Subsequently in a primate model of head injury Gennrelli reproduced similar injury and found that the rotation in the coronal plane caused maximum neurological impairment, coma time, diffuse axonal damage[4]. Coupled with a human neuropathological study that was published in the same journal issue of Annals of Neurology, the term diffuse axonal injury was coined[7].

However, the most path-breaking discovery of recent times has been the understanding that the axonal disconnection is not an immediate event, but is the pathological sequelae of axolemmal disruption which may or may not manifest later as axonal disconnection, thus potentially giving us time to salvage or limit injury.

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ILLUSTRATIVE CASE

78 yr male, post fall in a public wash room was found unconscious with evidence of vomiting. His admission Glasgow Coma Scale (GCS) score was E1M2V2-5/15. Preliminary CT scan/MRI/MR angio were normal apart from a very small slit like haemorrhage in the occipital horns. He was intubated on day 1 and extubated 12 hours later. However, 5 days later, he remained drowsy, although obeyed verbal commands. He had slurring of speech and post event amnesia.

Diffusion tensor imaging, fractional anisotropy and lumbar puncture did not reveal significant abnormalities. Almost 20 days later patient improved to a condition of near normalcy (modified Rankin score-0) and was discharged home. On regular follow-up three months after the incident, patient's wife stated that he has become forgetful and becomes agitated quite often. It was concluded that this patient probably had suffered traumatic axonal injury resulting in his protracted time to improvement and persisting functional abnormalities.

PATHOPHYSIOLOGY AND EVOLUTION OF AXONAL INJURY

Disruption of the axolemmal membrane as a result of trauma[8] followed by disruption of electrochemical homeostasis with passage of multiple ions along their concentration gradient, most important of which being calcium forms the basis of axonal injury[8-12].

Loss of oxidative phosphorylation and production of ATP as a result of intramitochondrial calcium overload also is a contributing factor to the pathology. The orderly activation of proteases like caspases and calpains are also disrupted, contributing to disruption of subaxolemmal membrane and neuronal cytoskeleton[13,14].

Traditional teaching says that axonal disconnection ultimately leads to neuronal cell death, however recent experimental data indicate that neurons may sustain proximal axonal injury and may not progress to cell death and in fact demonstrate attempt to regenerate synaptic contacts[15].

RELATION TO MILD TO MODERATE HEAD INJURY

There are various definitions for mild to moderate head injury. TBI is typically classified according to clinical criteria, specifically the lowest Glasgow Coma Scale (GCS) score in the first 48 hours (severe TBI = 3–8, moderate TBI = 9–12, mild TBI = 13 -15)[16]. By default focal brain imaging findings of contusion, hemorrhages, fractures, and hematomas are classified with moderate to severe head injury according to outcome studies by Williams and Levin[17]. Although axonal injury is microscopic and not easy to detect, its multifocal nature may have far greater clinical implications than overt focal damage. It is very well known that patient with mild to moderate head injury do have lasting cognitive impairment, attention deficits, memory losses, day time fatigue, depression, psychomotor slowing and other clinical features like the post-concussion syndrome. Although general cortical function is intact, any combination of these "mild" symptoms can be devastating for the patients and their families. These are probably sequelae of microscopic axonal damage as stated by many investigators[18].

More so even diffuse axonal injury is known to occur with mild to moderate head injury[19-21], even with a GCS of 14-15[18-22]. These are those patients who would be diagnosed as having a "significant concussional injury" which basically implies an axonal injury. Thus it does seem logical to say that the functional improvement and clinical sequelae of mild to moderate traumatic brain injury would depend on the quantity or severity of axonal injury and attempts to quantify the same would go a long way in establishing the functional prognosis of mild to moderate head injury. This is especially important to a country like India where the dynamics of family economics is dependent on a sole earning member in many cases. Hence judging the prognosis and the approximate time off work has huge financial implications.

DIAGNOSIS

The term axonal injury itself suggests that it is a form of microscopic injury and hence would probably not be picked up with routine CT scans, and probably MRI may be a better modality to diagnose the same.

Typical findings on CT scan would be small point hemorrhages (5-15 mm), sometimes referred to as 'micro bleeds' in the white matter, gray- white matter junction in frontal and temporal lobes, sometimes in corpus callosum and brain stem, traces of blood in ventricular system and around the mesencephalic areas[18,23-25]. However this is a complete underestimation of the burden of axonal injury with the above findings generally

seen in the severe form of diffuse axonal injury as many a times diffuse axonal injury is not picked up with the CT scans[19-20].

Fast T2- weighted spin echo sequences and flair sequences would detect subtle increase in brain water content, i.e. edema which may or may not be present in all cases of axonal injury especially those as result of mild to moderate head injury [26, 27]. Also the edema if any would be present only in the subacute or chronic phase as described in the pathobiology earlier. Gradient T2-weighted images may detect blood degradation products, especially in those patients with repeated falls and thus signifying earlier injury in patients presenting with fresh insult[28]. Depending on the MRI findings, diffuse axonal injury has been graded into three grades by Adams et al[29], the worst being the presence of all three, i.e. diffuse axonal injury, hemorrhage in the corpus callosum and lesion in the dorsolateral rostral brainstem which helps us estimate the severity of pathology and likelihood of survival.

NEWER IMAGING MODALITIES

Diffusion MRI is more sensitive in detecting increase in water content as compared to conventional MRI. However, it cannot be a substitute to conventional MRI as microbleeds are better detected with conventional MRI. Anisotropy based techniques seem to be more sensitive in detecting axonal injury even in mild head injury. Diffusion weighted imaging have known to detect axonal injury when other sequences have failed to do so [31, 32]. Disruptions of the normal orderly arrangement of the white matter axonal pathways are also picked up early with great deal of sensitivity by diffusion tensor imaging[33- 34]. There is also an emerging role of susceptibility weighted imaging and magnetization transfer imaging in the early detection and outcome prediction of axonal injury[35].

However these modalities are not free of false negatives as seen in the illustrative case. These ultra-sensitive modalities are also quite expensive. Moreover, in mild to moderate head injuries, there are no clear indications for the use of these expensive modalities of imaging. In the author's view, if research shows a robust relation between post-traumatic symptoms and lesions detected by MRI or its advancements we should consider using those as the modality even in mild head injuries as has been suggested for severe TBI by Rosa et al and many others recently, where multiplicity of corpus callosal lesions and brain stem lesions in MRI (not detected on CT) and prognosticated outcome and time to recovery to consciousness[36].

MANAGEMENT

At the time of writing this review there has been no evidence based effective treatments for the entity of axonal injury. In the acute phase local treatment guidelines as proposed by the brain trauma federation needs to be followed. A number of novel calcium channel blockers and antioxidants, uncoupling proteins and mitochondrial permeability transition pore inhibitors are in various phases of clinical trials. Although a 'magic bullet' has not yet been identified, the results of both preclinical and clinical studies are encouraging.

Among the various molecules under trial, cyclosporine A, a drug used in transplant management, has shown promise in treating many neuronal and axonal pathologies including sequelae of axonal injury[37-41]. A trial in phase 2 has been completed in this regards. Those patients with documented severe axonal injury should be referred to institutes with expertise in treating traumatic brain injury. Those patients with mild to moderate traumatic brain injuries but documented axonal injury by imaging could be managed on outpatient basis with proper neuropsychological assessment and rehabilitation[42-43]. Long-term follow-up is very important as the improvement in condition is a long-drawn process requiring multimodal management and rehabilitation measures. As most patients like the one in the case illustrated above regain functions, they would need more support from the surroundings and medical and paramedical professionals as they would likely face new challenges and newer environmental demands.

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