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Diffuse Axonal Injury (DAI) or (Diffuse Impact injury (DII) - Views and reviews

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1. INTRODUCTION

The initial clinical definition of DAI was posttraumatic loss of consciousness lasting longer than six hours. It was presumed in cases in which no mass lesion was present to explain the coma (Singleton et al. 2008). Classical cerebral concussion results in loss of consciousness which is transient and reversible –in a somewhat, arbitrary definition, the patient returns to full consciousness by six hours, although it is usually much sooner (Raj K Narayan, 1994).

Axonal injury is a non-specific term referring to damage to axon by any etiology. Traumatic axonal injury (TAI) is damage to axons caused by trauma and may be focal, multifocal or diffuse. Diffuse axonal injury (DAI) was first described as a clinicopathological syndrome in patient in patient unconscious from the time of trauma with wide spread traumatic axonal damage throughout the brain including the brain stem (Adams et al. 1989; Adams et al. 1977; Strich, 1956). It has been suggested recently that DAI should be referred to as diffuse traumatic axonal injury (diffuse TAI), (Geddes et al. 2010).

Thus it is a type of primary diffuse injury to brain following head injury. This type of injuries referred to by Adams and colleagues (Adams et al. 1989; Adams et al. 1977) was 1st clearly delineated by Strich in 1956 (Strich, 1956).

The population most at risk for sustaining DAI in some patient after sever TBI (traumatic brain injury) is likely to be young and male because it most likely occurs secondary to high velocity events. The sufferer is most commonly associated with severe disability and persistent vegetative state with lifelong and limited functional independence. Disability may cause a lot of financial impact.

2. PATHOLOGY

Three classic lesions in DAI are focal necrosis and /or hemorrhage, ischemic and tear in corpus callosum that are predominantly microscopic and hemorrhagic necrosis of the dorsal dorsolateral quadrant of rostral pons and reactive axonal swelling (Figure 1). These microscopic features are reactive axons ('Strich lesions' or retraction ball/bulb) and microglial clusters ('Stars'). These reactive axonal swelling secondary to distraction (shearing) of nerve fibers called

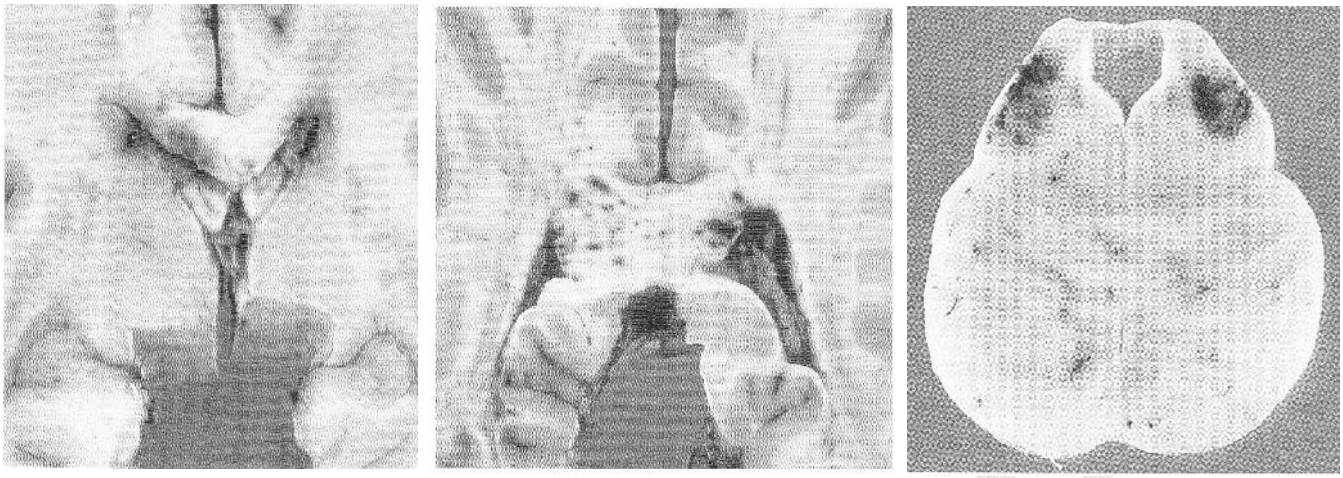

Figure 1

Features of DAI in corpus callosum, selenium and pons (Blumberg and Fukamachi, 2005)

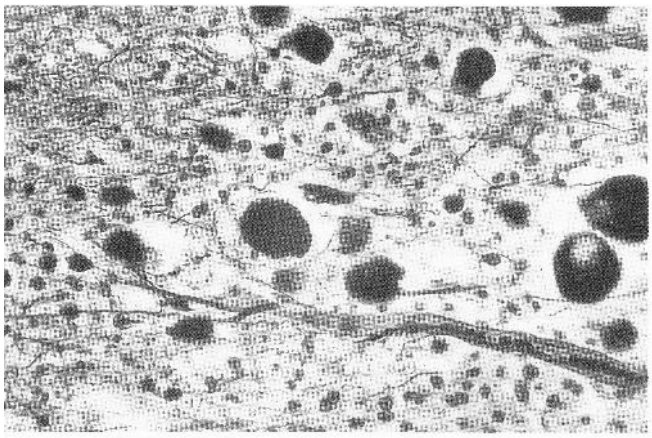

Figure 2

Strich lesions or retraction ball/bulb (Blumberg and Fukamachi, 2005)

Strich lesions (Figure 2). Later microglia migrates in to the area of axonal damage called microglial clusters (stars) and the debris laden macrophages are also found (Strich, 1961). Corpus callosum injury is caused by lateral stretching and may include minute hemorrhage to involving whole of corpus callosum. Pons lesions are also not due to direct impact but indirect lesion. Retraction ball have been demonstrated as early as 3 hours after injury. Small vessels like capillaries are also torn in DAI (Mc Cormick, 1966).

Pathological Grades : Gennarelli et al., (1982) classified DAI according to its severity Grade I ,only microscopic evidence of axonal injury in the para sagital white matter, Grade II, additional injury, focal abnormality(usually small hemorrhages) to corpus callosum, Grade III additional injury to dorsolateral mid brain, pons (brain stem), (Singleton et al. 2008). Sever the grading worse the prognosis. In study of 122 sever TBI, grade- I axonal injury noted in 10, grade II in 29, and grade III in 83 patients (Marion et al. 2003).

Markers of axonal damage: Amyloid precursor proteins (APP) that are normally transported along the axons, accumulates in damaged fibers and may be demonstrated by immunocytochemical methods. It is most reliable indicator and capable of detecting DAI within 1.75 hours to 3 hours of insult. Quantification of Dai is also possible with Axonal injury sector score (AISS). It is obtained by dividing standard brain sections in to 116 sectors and scoring the presence or absence of AI in each of these sectors to provide a score ranging from 0 to116 (Blumberg et al. 1995). Phosphorylated tau (a microtubule associated protein) accumulates in injured axon and cell bodies and even in CSF. Neurofilament proteins (68and 200-kDA) may be reduced in 3 hour post injury. Microtubule associated protein (MAP-2) show marked decreased in acute as well as in persistent DAI. It is also useful marker of dendritic pathology in cerebral ischemia (Blumberg and Fukamachi, 2005).

3. MECHANISM & PATHOPHYSIOLOGY

Diffuse axonal injury (DAI) appears to cause prolonged traumatic coma that is not due to mass lesion and is caused only by angular or rotational acceleration and not by contact phenomenon. It was found that rotation in coronal plane cause worst degree while in sagital plane the least degree and oblique in middle degree in neurological impairment. The amount and location of axonal injury probably determines the severity (depth and duration) of injury as well as quality of recovery. Most important discovery in recent times is delayed phenomenon in axonal disconnection and does not occur primarily at the time of injury therefore there are chances of development of therapy modify or reduce axonal injury in the window period. This has resulted in deviation from earlier concept of 'primary axotomy' to current concept of ''secondary axotomy. Initial perturbation is caused but not overt disruption

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Table 1

CT Scan in DAI (Marshall and Marshall, 1996)

SN	Category	Definition
1	DAI I(no visible abnormality)	No Intra cranial abnormality visible on CT Scan
2	DAI II	Cisterns are present with midline shift of 0-5 mm and/or --lesion density are present --no high or mixed density lesion of volume >25 ml is present --bone fragment and foreign bodies may be present
3	DAI III (Swelling)	Cisterns are compressed with midline shift 0-5mm no high or mixed density lesion of volume >25 ml is present
4	DAI IV (Shift)	Midline shift. 5mm, no high or mixed density lesion of volume >25 ml is present
	Evacuated mass lesion	Any lesion surgically removed
	Non Evacuated mass lesion	high or mixed density lesion of volume >25 ml , not surgically removed

of axonal membranes. It then initiates multiple pathological processes that results in cessation of axonal transport, degradation of the axonal cytoskeleton, and ultimate axonal disconnection in the hours and days after the injury. It certainly possible to have immediate disconnection if sear force is extraordinary but now it is thought that in majority of case axon remain physically intact after the initial injury. There multiple of mechanism responsible one of them is uncontrolled inward of calcium ions because of axonal perturbation. Increased intracellular calcium initiates multiple pathways. Calpains are calcium dependent proteases which become activated. This protease has numerous intra cellular targets and results in degradation on both neuronal and axonal cytoskeleton. Mitochondria are also essential to maintenance of intra cellular calcium levels, in addition to its role in intra cellular energy metabolism and oxidative phosphorylation. Increased uptake of calcium causes swelling of mitochondria and loss of electrochemical potential across the mitochondrial membrane. This causes loss of phosphorylation and cessation of energy production in form of adenosine triphosphate production (ATP). Mitochondrial swelling also causes opening of mitochondrial permeability transition pores resulting in release of cytochrome-c into the cytoplasm of the cells. This and other proteins activate caspases (cysteine proteases) essential for initiating apoptotic cell death. Caspase pathway (especially Caspase 3) is responsible for degradation of the subaxilemal cytoskeleton in setting of axonal injury. Therapeutic agents targeting each of these patho-physiological mechanisms of traumatic axonal injury (calpain activation, caspase activation, mitochondrial damage) are at various stages of preclinical testing. Current experimental data indicates that neurons may sustain proximal axonal injury and disconnection without evidence of cell death contrary to previous beliefs Neuron cells may initially show morphological sign of injury, but also demonstrate evidence of attempted regeneration of synaptic contact. It is hoped that surviving neurons sustaining axonal injury would allow them to be recruited by future therapies as a component of neurorehabilitation (Singleton et al. 2008). Almost all cases of DAI especially it's sever forms, arise from vehicular injury (impact to padded dash board resilient windshields, energy absorbing steering wheels) in which acceleration is long (Gennarelli and Meaney, 1996).

Most the case do not have lucid interval and also fracture of skull boneless frequently than in case of focal injury. But raised ICP, edema, and hypoxic damages are more frequent. Mean total index was striking as it is 8.3 in case DAI while 17.8 with other type of injury (Mc Cormick, 1996).

Clinically, patients are often encountered with prolonged post traumatic state in which there is loss of consciousness from the time of injury that continues beyond Six hours. This may be classified into mild, moderate and severe variety.

Mild DAI is a relatively uncommon, defined as that group in which coma lasting from 6 to 24 hours. It amounts to around 19 % of cases.

Moderate DAI is defined as coma lasting more than 24 hours without prominent brain stem signs. This is most common variety of DAI, comprising 45% of all cases of DAI.

Severe DAI occurs in vehicular accidents, comprising about 36% of all Patients with DAI. Patients are rendered deeply comatose and remain so for prolonged period of time. They often demonstrate evidence of decortications or decerebrations and often remains severely disabled, if they survive. These patient often exhibit autonomic dysfunctions such as hypertension, hyperhydrosis and hyperpyrexia. Previously thought to have primary brain stem injury, it is now believed that diffuse axonal injury throughout the brain is the more common pathologic basis.

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Investigation of DAI: CT scan detected scattered petechial hemorrhages, most commonly at cortical gray-white junction for details of CT scan findings (Table 1). At present MRI detects with high sensitivity or Neurophysiological testing such as somatosensory evoked potential (SSEP) or brain stem auditory evoked potential (BAEPs) may be done. MRI is also more sensitive in detecting non hemorrhagic injury and brain stem injury than CT scan. Diffusion weighted images (DWI) rely on detection of restricted diffusion of water (increased anisotropy) demonstrated to identify lesions associated with DAI that are not detected on any other MRI sequences. Diffusion tensor images (DTI) based on decreased restriction on water movement (deceased anisotrophy) has been found to be especially sensitive to disruption (Singleton et al. 2008).

Treatment: Management till now centers around treatment of raised ICP either medical or surgical and role of DC has already been discussed above. Till 2010 there have been no effective treatment reported for DAI. Current clinical efforts are primarily focused on limiting secondary injury. A recently concluded phase II clinical trial of the immunophilin legend cyclosporine A (Cs A) has shown preliminary evidence improvement in brain metabolic parameters. Cs A is presently known for its role in prevention of transplant rejection. In experimental setting it has shown to mitigate a variety of posttraumatic neuronal and axonal pathologies, including DAI. Its neuroprotective mechanisms are – (1) prevention of mitochondrial permeability in response to elevated intra axonal calcium (2) inhibition of Calcineurin, a protein phosphatase that has shown to reduce DAI independent of mitochondrial effects.

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