Journal of Clinical Neuroscience 16 (2009) 614–619

Contents lists available at ScienceDirect

Journal of Clinical Neuroscience

journal homepage: www.elsevier.com/locate/jocn

Review

Diffuse axonal injury: Novel insights into detection and treatment

Xue-Yuan Li [a], Dong-Fu Feng [b,*]

[a] Department of Neurosurgery, No. 3 People's Hospital Affiliated to Shanghai Jiao Tong University College of Medicine, Shanghai 201900, China
[b] Department of Neurosurgery, No. 3 People's Hospital Affiliated to Shanghai Jiao Tong University College of Medicine, No. 280 Mo-He Road, Shanghai 201900, China

ARTICLE INFO

Article history:
Received 30 January 2008
Accepted 1 August 2008

Keywords:
Biochemical markers
Coma
Diffuse axonal injury
Neuroimaging
Specific treatment

ABSTRACT

Diffuse axonal injury (DAI) is one of the most common and important pathologic features of traumatic brain injury. The definitive diagnosis of DAI, especially in its early stage, is difficult. In addition, most therapeutic agents for patients with DAI are non-specific. The CT scan is widely used to identify signs of DAI. Although its sensitivity is limited to moderate to severe DAI, it remains a useful first-line imaging tool that may also identify co-morbid injuries such as intracerebral hemorrhage. Recently, investigations have sought to apply advanced imaging techniques and laboratory techniques to detect DAI. Meanwhile, some potential specific treatments that may protect injured axons or stimulate axonal regeneration have been developed. We review some new diagnostic technologies and specific therapeutic strategies for DAI.

1. Introduction

Diffuse axonal injury (DAI) in patients with traumatic brain injury (TBI) is associated with significant morbidity, and often leads to significant neuropsychological sequelae and burdensome health care costs. DAI typically occurs when the head is subjected to shear-strain forces, with most lesions emerging at the interface between regions of the brain that have different tissue densities, such as at the junctions between gray and white matter. Classically, although neuroimaging can detect features such as petechial hemorrhages suggestive of DAI, a definitive diagnosis could only be established by immunostaining for β-amyloid precursor protein (β-APP) at autopsy. However, recent advances in both neuroimaging and laboratory techniques have allowed for more subtle lesions to be detected earlier, potentially allowing the diagnosis of DAI in the acute phase. This introduces the possibility of DAI treatment early in the course of the injury, which has the potential to positively affect outcome. In this review, we explore the potential value of new diagnostic technologies in identifying DAI, and suggest potential clinical applications.

2. Coma as an indicator of DAI

DAI is characterized clinically by the rapid progression to coma in the absence of specific focal lesions. DAI is arguably the major cause of post-traumatic unconsciousness. In this setting, loss of consciousness may last only minutes, or it may result in prolonged coma, depending on the nature and severity of the underlying injury. In a hallmark study, Gennarelli et al. demonstrated that DAI can be the sole contributor to post-traumatic unconsciousness. They observed that non-human primates developed immediate and prolonged coma in the absence of focal lesions when subjected to non-impact rotational acceleration.[1] DAI was the only type of tissue injury noted in pathological examination of these animals. In subsequent studies, other authors used Adam's classification to categorize DAI as mild, moderate, or severe. They proposed that any acceleration or deceleration could cause a mild case of DAI, in which brief loss of consciousness occurred.[2]

At its most severe, patients with DAI who survive rapidly lapse into coma, and remain unconscious, vegetative, or severely disabled until they die. The duration of coma in TBI patients correlates with the severity of DAI lesions identified by neuroimaging. In one prospective study, in which 21 DAI patients underwent MRI within 24 hours of injury, a positive correlation was established between the duration of unconsciousness and the maximal signal intensity of the corpus callosum.[3] This suggests that coma duration in DAI may be an indicator of the extent of axonal damage.

However, a recent report described a patient with findings consistent with DAI on MRI who manifested no coma in the first 11 hours of injury, challenging the classical association of DAI with rapid-onset coma.[4] He et al. reported that coma depends not only on the ultimate distribution of axonal pathology, but also on the plane of the causative rotational head acceleration.[5] Axonal injury in the brainstem appears to be one of the primary factors responsible for the generation of coma in DAI.[6] Therefore, based on MRI findings, as well as on the depth and duration of coma after TBI, one can infer the existence of DAI and to some degree estimate its severity, but a definitive diagnosis cannot be established pre-mortem.

* Corresponding author. Tel./fax: +86 021 56693614.
E-mail address: feng_df@yahoo.com (D.-F. Feng).

0967-5868/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jocn.2008.08.005

3. Neuroimaging features of DAI

3.1. CT scanning and conventional MRI

Conventional MRI (cMRI) (MRI using T1-weighted, T2-weighted, fluid attenuated inversion recovery [FLAIR] and gradient echo sequences) is more sensitive than CT scanning for detecting axonal injury-related lesions, although both methods are widely used. CT examination, still the initial imaging study of choice for head-trauma patients, is readily available, fast, and sensitive in detecting hemorrhage. In contrast, cMRI allows the nature and extent of both hemorrhagic and non-hemorrhagic cerebral tissue injuries to be determined at higher resolution, especially within the posterior fossa and deep white matter. However, acquiring the appropriate sequences takes significantly longer than with CT scans; in addition, many patients are too unstable to have an MRI upon initial presentation. In the most severe cases of DAI, axonal pathology is often accompanied by intraparenchymal hemorrhage, which is clearly visible on CT. Early hemorrhagic lesions are associated with hypertension, and are frequently surrounded by hypodense areas representing cytotoxic edema, axonal destruction, or tissue necrosis.[7] However, when used to evaluate mild to moderate DAI, cMRI is demonstrably superior to CT scanning in detecting petechial hemorrhages and non-hemorrhagic lesions. Thus, CT and MRI each have their own benefits in the clinical assessment of head-trauma patients.

Hemorrhagic DAI lesions vary in signal intensity depending on the age of the blood involved and the sequence employed. By detecting paramagnetic properties of iron-containing heme moieties, gradient recovery echo (GRE) images are very sensitive to microhemorrhages. GRE detects a greater number of small hemorrhagic lesions than other sequences, with the results showing a positive correlation with the Glasgow Coma Scale score (GCS).[8] GRE is also able to detect all areas responsible for focal neurological signs 1 month after injury. Non-hemorrhagic lesions are typically more evident on T2-weighted imaging, particularly FLAIR sequences, which allow a better visualization of injured tissue by reducing signal interference from cerebrospinal fluid (CSF). In one prospective study,[9] 33 patients with a normal CT scan, but abnormal neurological status, were examined with cMRI within 48 hours. The authors noted that cMRI revealed more non-hemorrhagic lesions than CT scans, and that the presence of non-hemorrhagic lesions was associated with a relatively good clinical outcome. In contrast, in another study, which used FLAIR to quantify the affected white matter volume within 2 weeks of injury, total DAI volume was correlated with patient outcome, as measured by the Glasgow Outcome Scale - Extended. The authors concluded that this method could be used to stratify injury severity.[10]

Clearly, the use of CT scanning and MRI has greatly improved the detection of pathological tissue changes in DAI. However, both CT and MRI probably underestimate the extent of axonal damage, as most of this damage is microscopic. This is supported by the observation that many patients with severe TBI have minimal changes detected by CT scans or MRI. Therefore, recent investigations have sought to apply advanced imaging techniques to the measurement of tissue injury in DAI.

3.2. Advanced MRI techniques

Newer and more sensitive imaging techniques better visualize tissue damage and monitor dynamically the intracranial metabolic changes following head trauma.

Diffusion-weighted imaging (DWI) was initially investigated in the context of DAI because of its ability to detect the cytotoxic edema occurring after acute stroke. Head trauma leads to an alteration of local diffusion, and DWI is more sensitive than cMRI for the detection of DAI. In a study that examined 25 patients with DAI within 48 hours of the inciting trauma, DWI identified 310 shear injuries consistent with DAI out of 427 lesions counted by all sequences combined (followed by T2/FLAIR [n = 248] and GRE [n = 202]). Furthermore, DWI uncovered 70 lesions that were not detected by cMRI. Most DWI-positive lesions showed decreased diffusion (65%), potentially indicating cytotoxic edema.[11] However, one recent study reported that DWI was superior to FLAIR in evaluating DAI lesions of the fornix, while in the corpus callosum and gray-white matter junction, DWI had no advantage.[12] These conflicting findings may be at least partially due to differences in timing. DWI imaging in the former study was typically performed within 20 hours, whereas in the latter, the time at which patients underwent imaging was much more variable (a range of 20 hours to14 days; mean 3.7 days). In DAI regions there is an evolution from restricted diffusion (cytotoxic edema) to unrestricted diffusion (vasogenic edema).[13]

Some studies have recently attempted to determine the relationship between various DWI variables and clinical status. Zheng et al. reported that mean apparent diffusion coefficient (ADC) values were positively correlated with the duration of coma in DAI patients.[14] Ezaki et al. found that DWI could predict clinical outcome in DAI patients.[15]

Diffusion tensor imaging (DTI) may be more sensitive to DAI lesions than cMRI (studies well summarized by Hurley[15]). The most informative neuroanatomic locations in which to apply DTI for the identification of DAI have been debated. One study, involving 20 patients and 15 healthy controls, measured the fractional anisotropy (FA, a scalar measurement of diffusion anisotropy, generally considered an index of injury to white matter) values of multiple locations, and correlated these with clinical scores. The FA values in the splenium and internal capsule of patients were correlated with both the acute GCS at the time of injury and the Rankin scores at the time of discharge. No similar correlation was observed for the thalamus and putamen.[16] In contrast, another investigation recruited 20 patients and 14 aged-matched controls in order to investigate global white matter integrity. Mean FA histograms were globally diminished compared with controls in all cases, including mild TBI patients. In addition, the FA parameters were correlated with the injury severity index (by GCS) and with post-traumatic amnesia (PTA).[17] The authors concluded that, in detecting white matter injury, the whole-brain white matter approach may have no clear superiority over a regional approach, but that quantifying the white matter damaged may provide additional prognostic information.

Other investigators studied the specificity of DTI for DAI. Donald et al. used DTI to analyze the impact-induced mouse model of DAI. This allowed them to directly compare DTI findings with a histological assessment of axonal injury. They noted that axial diffusivity and relative anisotropy were reduced in the pericontusional corpus callosum and external capsule with normal cMRI. Changes in the relative anisotropy were negatively correlated with the density of β-APP. The anterior commissure displayed no reduction of axial diffusivity and relative anisotropy, consistent with the absence of histological evidence of axonal injury.[18] This suggests that DTI is highly sensitive to axonal injury, and in addition may have a high negative predictive value. The sensitivity of DTI in this context has been corroborated in another study, which noted that the axial diffusivity derived from DTI accurately matched the pattern of axonal damage.[19] Donald et al. found that a decline in axial diffusivity was apparent within 3 hours in areas of histologically confirmed axonal injury,[18] which suggests that DTI may be a sensitive tool in detecting DAI in the superacute phase.

A modification of GRE, susceptibility weighted imaging (SWI), increases the ability of GRE to detect hemorrhagic lesions, thereby improving the detection of DAI by illuminating minute