

# Traumatic Axonal Injury in Concussion

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Traumatic axonal injury (TAI) indicates the tearing of axons by indirect shearing forces during acceleration, deceleration, and rotation of the brain or direct head trauma. Since the 1960s, histopathological ones after autopsy have revealed TAI in patients with concussion who died from other causes. The diagnosis of TAI in live patients with concussion is limited because conventional brain MRI is not sensitive to detecting TAI in concussion.

concussion

mild traumatic brain injury

diffusion tensor imaging

## 1. Ambiguity of Diagnostic Criteria for Concussion and Diffuse Axonal Injury

Head trauma is defined as concussion when loss of consciousness (LOC) following a head trauma lasts less than six hours but it is defined as a diffuse axonal injury when LOC lasts six hours or more [1][2]. On the other hand, the six-hour LOC criterion to distinguish between concussion and diffuse axonal injury is deficient of convincing evidence because TAI lesions have been detected in concussion [3][4][5]. Gennarelli, which has been frequently cited as the reference of this criterion, did not include a reference for the origin of the criterion [2], but another one by Gennarelli et al. reported that approximately half (46.7%) of monkeys focused that exhibited LOC for less than six hours after whiplash had axonal injury lesions on a histopathological test [3]. Others were detected axonal injury lesions through autopsy in patients with concussion or mild TBI who died of other diseases [6][7][8]. Furthermore, axonal injury lesions were detected in conventional brain MRI in 12.5–30% of patients with mTBI; Mittl et al. (1994) and Topal et al. (2008) detected diffuse axonal injury lesions in conventional brain MRI in 30% and 12.5%, respectively [4][5].

## 2. Limitation of Conventional Brain MRI in the Detection of TAI in Concussion

In individual patients with concussion, the absence of neural injury has been determined mainly based on normal findings in conventional brain MRI. However, the low resolution of conventional brain MRI compared to the neuron number of the human brain can be problematic. In detail, there are at least ten billion neurons in the human brain, and a brain MRI scan consists of approximately 300,000 voxels (a voxel refers to a point on a three-dimensional plane) [1][9]. Based on these values, each voxel within a brain MRI scan would indicate the status of at least approximately 30,000 neurons. This low resolution of brain MRI makes it difficult for a brain MRI to accurately reflect the state of neural injury. Thus, normal findings in a conventional brain MRI may not indicate whether the

brain is in a normal state [1][9]. Because of this limitation of conventional brain MRI, only approximately 50% of axonal injury lesions can be detected, even in patients with diffuse axonal injury [10][11][12][13][14].

## 3. Evidence of Organic Brain Injury in Concussion

Recovery from concussion should be complete without sequelae because it is a transient dysfunction of the brain [15][16]. However, a significant proportion of patients with concussion show sequelae three months after onset. These patients were diagnosed with post-concussion syndrome, which has been recognized as a psychological problem [15][16][17][18][19]. Rutherford et al. reported that approximately 15% of patients with concussion showed sequelae one year after concussion [19]. In contrast, McMahon et al. reported that one year after concussion, 82% of patients had at least one symptom of post-concussion syndrome [20]. After introducing DTI, many were showed that TAI is the underlying pathophysiology of post-concussion syndrome [21][22]. On the other hand, opinions critical of the terms concussion and mTBI, which indicate a benign condition, have been suggested. Some researchers suggested that the terms concussion and mTBI should be avoided because many of these patients show severe sequelae and exhibit heterogeneous clinical features, ranging from mild to severe [20][23][24][25].

Many have been provided evidence of organic brain injuries using various evaluation methods, such as single-photon emission computed tomography, positron emission tomography, evoked potential testing, electroencephalography, functional MRI, magnetoencephalography, and blood biomarkers [26][27][28][29]. However, these evaluation methods have limitations because none can show the definite pathology or localization of a lesion at the subcortical white matter level.

## 4. History of Traumatic Axonal Injury in Concussion

TAI is a pathological diagnostic terminology. Thus, a histopathological one via a brain biopsy is required to confirm the TAI of a neural structure in patients with concussion [9]. Conversely, brain biopsy in patients with concussion is impossible because concussion is not a life-threatening disease [9]. As a result, a precise diagnosis of TAI in live patients with concussion can be limited. Since the 1960s, several have been demonstrated TAI via autopsy in patients with concussion who presented no radiological evidence of brain injury [6][7][8]. In 1994, Blumbergs et al. detected TAI lesions via autopsy in the brain of five patients with concussion who died of other diseases [7]. However, the diagnosis of TAI in live patients with concussion was limited before the introduction of DTI because conventional brain MRI is not sensitive to the detection of TAI in concussion.

Since the 1980s, many researchers, including Povlishock, began to use the term "TAI" in their histopathological ones using animal brains [9][30][31][32][33]. Povlishock et al. observed axonal injuries upon a histopathological test of cat brains that experienced minor head injury via a fluid-percussion injury, but the cats did not show clinical abnormalities [30]. It was assumed that the absence of clinical abnormalities in animals that exhibited axonal injuries in the brain might be because no more than one hundred to one hundred and fifty axons were affected, even though the corticospinal tract contains several hundred thousand axons in any animal [30]. Furthermore, they

suggested that asymptomatic concussion patients might have a minor axonal injury and that post-concussion syndrome might be related to this type of axonal injury [30]. Others were reported the possible presence of asymptomatic axonal injury in concussion or mTBI [31][32]. Consequently, Poblishock et al. reported that axonal injury is a common finding of all TBIs [31]. Moreover, the distribution and number of injured axons increase with the increasing severity of the trauma in mild, moderate, and severe TBI [33].

The history of the use of the term TAI with regard to the term “diffuse axonal injury” has caused some confusion in the clinical field [9][34]. Adams et al. (1982) began to use the term “diffuse axonal injury”, which defined microscopic axonal injuries in the white matter of the cerebral hemisphere, corpus callosum, and brainstem caused by mechanical forces during TBI [9][34][35]. Instead of diffuse axonal injury, “TAI” or “diffuse TAI” was used to correct the confusion in the term “diffuse”, because the location of the lesions of diffuse axonal injury was not diffuse but multifocal, and diffuse did not include the meaning of trauma as the etiology of axonal injury [9][34][36][37][38][39]. Generally, the traditional definition of diffuse axonal injury refers the patients with severe and prolonged coma at the onset of head trauma with poor outcomes [9][34][36][37][38][39]. The term “TAI” began to be used for these injuries instead of diffuse axonal injury because more limited patterns of axonal injury than classical diffuse axonal injury were observed in milder TBI with the introduction of DTI [9][34][36][37][38][39].

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