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Traumatic Axonal Injury in Patients with Mild Traumatic Brain Injury

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Abstract

Mild traumatic brain injury (TBI) is a subtype of TBI that is classified by the severity of head trauma, whereas traumatic axonal injury (TAI) is a diagnostic term with a pathological meaning. In this chapter, TAI in patients with mild TBI is described in terms of definition, history, and diagnostic approach. The presence of TAI in patients with mild TBI has been demonstrated by autopsy studies since the 1960s. However, because conventional brain CT or MRI are not powered with contrast resolution to determine TAI in mild TBI, diagnosis of TAI in live patients with mild TBI was impossible. Since the introduction of diffusion tensor imaging, hundreds of studies have demonstrated TAI in live patients with mild TBI in the 2000s. The precise diagnosis of TAI in patients with mild TBI is clinically important for proper management and prognosis prediction following mild TBI. Several requirements are necessary for diagnosis of TAI in mild TBI: first, head trauma history; second, development of new clinical symptoms and signs after head trauma; third, evidence of TAI of the neural tracts on diffusion tensor imaging or diffusion tensor tractography; and fourth, coincidence of the newly developed clinical features and the function of injured neural tracts.

Keywords: diffusion tensor imaging, diffusion tensor tractography, mild traumatic brain injury, traumatic axonal injury, concussion

1. Introduction

Traumatic brain injury (TBI) is a major cause of disability in adults, and is classified as mild, moderate, and severe according to the severity of head trauma [1]. Mild TBI poses a significant public health problem: it composes 70–90% of all TBI [1–4]. The incidence of hospital-treated patients with mild TBI is 100–300/100,000 population although the true population-based rate including mild TBI not treated in hospitals is estimated above 600/100,000 [1–4]. Mild TBI

Pathoanatomy			
Diffuse		Focal	
Concussion		Contusion	
Traumatic axonal injury/diffuse axonal injury		Penetrating	
Blast		Hematoma	
Abusive head trauma		- Epidural	
		- Subarachnoid	
		- Subdural	
		- Intraventricular	
		- Intracerebral	
Severity of head trauma	Loss of consciousness	Post-traumatic amnesia	Glasgow Coma Scale
Mild	≤30 min	≤24 hours	13–15
Moderate	>30 min, ≤24 hours	>24 hours, ≤7 days	9–12
Severe	> 24 hours	>7 days	3–8

Table 1. Traumatic brain injury subtypes.

and concussion (a transient disorder of brain function without long-term sequelae) have been used interchangeably, although the two terms have different definitions and belong to different subtypes of TBI (**Table 1**) [5–7].

Since the 1980s, the term “traumatic axonal injury (TAI)” that describes impaired axoplasmic transports, axonal swelling and disconnection after the head trauma, including mild TBI, has been used in pathological studies using animal brain [8–11]. Since the 1960s, pathological studies using autopsy reported axonal injury in patients with mild TBI or concussion [12–14]. However, because conventional brain CT or MRI are not powered with contrast resolution to determine TAI in mild TBI, diagnosis of TAI in live patients with mild TBI was impossible for a long time. Since the development of diffusion tensor imaging (DTI) in the 2000s, many researchers demonstrated TAI in live patients with mild TBI [15–85]. Because mild TBI and TAI are different TBI subtypes, the precise diagnosis of TAI in patients with mild TBI is clinically important for proper management and prognosis prediction (**Table 1**) [6, 7].

In this chapter, TAI in patients with mild TBI is described in terms of definition, history, and diagnostic approach.

2. Traumatic axonal injury in patients with mild traumatic axonal injury

2.1. Definition and problem of the term “mild traumatic brain injury”

The American Congress of Rehabilitation Medicine in 1993 defined mild TBI as a traumatically induced physiological disruption of brain function resulting from the head being struck or

striking an object, or an acceleration and deceleration movement of the brain, as manifested by at least one of the following: any period of loss of consciousness up to 30 min, post-traumatic amnesia not exceeding 24 hours, and an initial Glasgow Coma Scale score of 13–15 [86–89]. Blast may also cause mild TBI [90].

Opinions critical of the use of the term “mild TBI,” as indicating a benign condition, have been expressed [5, 91, 92]. In 2012, Rapp et al. insisted that mild TBI is a category mistake because of the heterogeneity of the clinical population and features, and the complex idiosyncratic time course of the appearance of these deficits in patients with mild TBI [92]. Subsequently, McMahon et al. reported that the term “mild TBI” is a misnomer because some of the patients with mild TBI show severe neurological sequelae [91]. In 2015, Sharp and Jenkins insisted that mild TBI is not always a benign condition as its name implies and patients with mild TBI sometimes fail to recover [5]. These critical opinions appear to stem from the observations of concurrent TAI in patients with mild TBI that cannot be detected on conventional brain CT or MRI. Such lesions have been described by hundreds of DTI studies since the 2000s [15–85].

2.2. Definition and diagnostic history of traumatic axonal injury in mild TBI

Neural axons in the white matter are particularly vulnerable to diffuse head trauma due to mechanical loading of the brain during TBI [8, 93]. TAI, a pathological term, is defined as tearing of axons due to indirect shearing forces during acceleration, deceleration, and rotation of the brain, or direct head trauma [6, 9, 10, 15–23, 94, 95].

Since the 1980s, many researchers, including Povlishock, have used the term “TAI” in their pathological studies using animal brain [8–11]. In the human brain, several studies have demonstrated trauma-related axonal injury in pathological autopsy studies of patients who died of other causes following TBI, including concussion or mild TBI, since the middle of the last century [12–14, 96]. However, due to insensitivity of conventional brain MRI for detection of TAI in mild TBI, diagnosis of TAI in live patients with mild TBI was impossible for a long time. In the 1990s, the development of DTI opened a new era for diagnosis of the subcortical white matter pathology in the live human brain. Because DTI provides invaluable information about subcortical white matter that cannot be obtained by conventional MRI, DTI was initially used to detect white matter pathology undetectable by conventional CT or MRI in brain pathologies such as cerebral palsy, hypoxic-ischemic brain injury, and congenital brain disease [97–99]. Since Arfanakis’s study in 2002, TAI has been demonstrated in hundreds of DTI studies in mild TBI [15–85]. As a result, DTI become an important diagnostic tool for TAI in patients with mild TBI, particularly in patients whose conventional brain CT or MRI is negative.

The history of the use of term TAI with regard to the term “diffuse axonal injury (DAI)” has given rise to some confusion [6]. Adams et al. began to use the term “DAI” by defining DAI as the presence of microscopic axonal injury in the white matter of the cerebral hemisphere, corpus callosum, and brainstem caused by mechanical forces during head injury [100–102]. After that, instead of DAI, “TAI” or “diffuse TAI” was used to correct the mistaken term “diffuse” (because the distribution of the lesions of axonal injury is not diffuse but multifocal), and to include the meaning of trauma in terms of the etiology of axonal injury [6–8, 93]. Generally, the traditional definition of DAI indicates patients in profound and prolonged coma at the onset of

head trauma, and who suffer a poor outcome [6–8, 93, 102, 103]. Because more restricted patterns of axonal injury than the traditional DAI were detected in milder TBI with the development of DTI, the term “TAI” is used for these more limited injuries: in practice, TAI indicates milder injury than DAI [6–8, 93, 98, 103].

2.3. Comparison of diffusion tensor imaging and diffusion tensor tractography in detecting TAI in mild TBI

The left corticospinal tract shows partial tearing (arrow) at the subcortical white matter. When a researcher measures diffusion tensor imaging parameters using the region of interest (ROI) method, if the ROI is placed in the partially torn area (B), traumatic axonal injury of the left corticospinal tract can be detected, whereas if the ROI is placed in the normal-appearing area (D), traumatic axonal injury of the left corticospinal tract cannot be detected.

Two methods are used to detect TAI in mild TBI: (1) region of interest (ROI) method: measurement of DTI parameters in a certain ROI of the brain, and (2) diffusion tensor tractography (DTT) for the neural tracts (**Figure 1**). DTT allows for visualization and estimation of the neural tracts three dimensionally by reconstruction from DTI data: measurement of DTT parameters and configurational analysis of the reconstructed neural tracts [19, 20, 24–56, 61, 72, 98]. Many more studies have used the ROI method than DTT; however, this method can yield false results for the following reasons. First, high individual variability of the anatomical location of the neural tracts in the human brain can lead to measurement of DTI parameters in a false location for the target neural tract, especially in compact areas such as the corona radiata, posterior limb of the internal capsule, or brainstem [104]. In addition, the results can differ depending on whether a ROI is placed in a TAI lesion (for example, a partially torn area) or normal-appearing area. For example, when a neural tract was partially torn by TAI following mild TBI, if the ROI was placed in the normal-appearing area, TAI cannot be detected using the ROI method although this patient had TAI following mild TBI (**Figure 1**). Second, high interanalyzer variability of the ROI method can lead to false results [105].

By contrast, DTT for reconstruction of the neural tracts usually employs a combined ROI method that reconstructs only neural fibers passing more than two ROI areas. The ROI areas and reconstruction conditions for the neural tracts are well defined for each neural tract [6, 50, 106–113]. High repeatability and reliability of DTT method for the neural tracts have been demonstrated in many studies [6, 24, 50, 106–111, 113]. Therefore, experienced analyzers can reconstruct the neural tracts without significant inter- and intra-analyzer variation. The main advantage of DTT over DTI is that the entire neural tract can be evaluated in terms of DTT parameters, including fractional anisotropy, mean diffusivity and tract volume, and configurational analysis. Fractional anisotropy value indicates the degree of directionality of microstructures, such as axons, myelin, and microtubules, while mean diffusivity value suggests the magnitude of water diffusion [114]. Tract volume is determined by counting the number of voxels contained within a neural tract [114]. Therefore, a significant decrement of fractional anisotropy or tract volume, or increment of mean diffusivity compared with normal subjects, indicates injury of a neural tract. In addition, on configuration analysis of the

Figure 1. Possible false measurement of diffusion tensor imaging parameters in a partially torn corticospinal tract in a patient with mild traumatic brain injury.

reconstructed neural tracts, abnormal findings including tearing, narrowing, or discontinuation have been used to detect TAI of the neural tracts in patients with mild TBI (**Figure 2**) [19, 20, 24, 26–37, 39–56]. As a result, DTT would be better than DTI to detect TAI in a neural tract in an individual patient. More than 30 papers have demonstrated TAI in individual patients with mild TBI in the corticospinal tract, corticoreticulospinal tract, spinothalamic tract, fornix, cingulum, optic radiation, ascending reticular activating system, papez circuit, pre-fronto-thalamic tracts, inferior cerebellar peduncle, corticofugal tracts form the secondary motor area, arcuate fasciculus, corticobulbar tract, and dentatorubrothalamic tract [19, 20, 24, 26–37, 39–56]. However, DTT may underestimate the neural tracts due to regions of fiber complexity and crossing that can prevent full reflection of the underlying fiber architecture [105, 115, 116]. In addition, TAI on DTT often cannot be discriminated from abnormalities by previous head trauma, other concurrent neurological diseases, aging, or immaturity, although some findings suggest characteristic features of TAI in several neural tracts [26, 28, 29, 39, 48, 51–54].

Figure 2. Configurational analysis of the spinothalamic tract in patients with mild traumatic brain injury.

2.4. Diagnostic approach of traumatic axonal injury in patients with mild TBI

TAI is a diagnostic term with a pathological meaning; therefore, pathological study by brain biopsy is required to confirm TAI of a neural tract in patients with mild TBI. However, performing brain biopsy for an injured neural tract in patients with mild TBI is impossible because mild TBI is not a life-threatening disease like, for example, brain tumor. The sensitivity and specificity of DTT for diagnosis of TAI of a neural tract in patients with mild TBI can be calculated only through direct comparison of DTT findings of an injured tract with the pathological results of brain tissue, if we accept the latter as the diagnostic “gold standard.” As a result, precise demonstration of sensitivity and specificity of DTT for diagnosis of TAI of an injured neural tract in live patients with mild TBI is impossible. However, in 2007, Mac Donald et al. demonstrated that TAI on pathological and DTI results agree in a mouse model of mild TBI that showed normal findings on conventional MRI [117]. They concluded that DTI is highly sensitive for detection of TAI and conventional MRI is not as sensitive as DTI for axonal injury [117].

There are more than 30 recent papers that reported TAI in individual patients with mild TBI using DTT [19, 20, 24, 26–37, 39–56]. The methods to diagnose TAI of the neural tracts of the above studies can be summarized as follows (**Flow Sheet 1**). First, head trauma history compatible with mild TBI is required. According to the definition of mild TBI from the American Congress of Rehabilitation Medicine, the patient must have a head trauma history with three conditions of mild TBI: loss of consciousness, post-traumatic amnesia, and Glasgow Coma Scale [86]. If a patient did not suffer loss of consciousness, any alteration in mental state (feeling dazed, disoriented, or confused) at the time of the accident is necessary. Second, development of new clinical symptoms and signs after head trauma is required. The patient must show new clinical features after the head trauma, which were never observed before the head trauma. The possibility of delayed onset of the clinical symptom due to secondary axonal injury that refers to a condition in which axons were not damaged at the time of injury, but undergo axonal injury caused by the sequential neural injury process of an injured neural tract, should also be considered [9, 10, 24, 26, 27]. Third, evidence of TAI of a neural tract on DTT is required [19, 20, 24, 26–37, 39–56]. TAI of a neural tract can be detected by configuration (tearing, narrowing, or discontinuation) or DTT parameters (significant decrement of fractional anisotropy or tract volume, or increment of mean diffusivity) on DTT for a neural

Flow Sheet 1. Diagnostic approach of traumatic axonal injury of a neural tract in patients with mild traumatic brain injury.

tract (**Figure 2**). Fourth, DTT abnormality by previous head trauma, concurrent neurological disease, aging, immaturity, or artifact of DTT should be ruled out. In addition, the newly developed clinical features and the function of the injured neural tracts must coincide. Fifth, other pathologies including peripheral nerve injury, spinal cord injury, and musculoskeletal problems should be ruled out through other studies such as electromyography study, radiological study, or ultrasonography. Additionally, improvement of a clinical symptom with management of an injured neural tract could be an additional evidence for TAI. For example, when a patient develops central pain due to injury of the spinothalamic tract following mild TBI, and if the patient's pain improves with the administration of specific drugs for central pain, it would be an additional evidence for TAI in this patient. In addition, the clinical features and DTT findings of other neural tracts should be considered because TAI usually occurs in multiple neural tracts following diffuse head trauma like mild TBI [29, 30, 34].

For example, a 43-year-old female patient suffered injury from a car accident. She hit her head on the seats with acceleration-deceleration injury while sitting in a passenger seat in a minibus after a collision with a car from behind. She had no head trauma history, and findings were consistent with the three conditions of mild TBI [86, 87]. Since the head trauma, she noticed memory impairment, mild weakness of both hands, and central pain of the entire body. On DTT, the injuries of cingulum (discontinuations of both anterior cingula), the fornix (discontinuation of the left fornical crus), corticospinal tract (partial tearing at the subcortical white matter of both corticospinal tracts), and spinothalamic tract (partial tearing of the left spinothalamic tract) were detected (**Figure 3**). In this patient, TAI by this car accident was confidently diagnosed by the head trauma history, development of new clinical features, and injury evidence of the various neural tracts on DTT. The patient provided written informed consent.

Figure 3. Traumatic axonal injuries of several neural tracts in a patient with mild traumatic brain injury. (->:traumatic axonal injury, *suspicious traumatic axonal injury).

3. Conclusion

In this chapter, TAI in patients with mild TBI is described in terms of definition, history, and diagnostic approach. Precise diagnosis of TAI in patients with mild TBI is clinically important. The introduction of DTI has enabled diagnosis of TAI in the live patients with mild TBI [15–85]. Several requirements are necessary for diagnosis of TAI in patients with mild TBI: head trauma history, development of new clinical symptoms and signs after head trauma, evidence of TAI of the neural tracts on DTI or DTT, and coincidence of the newly developed clinical features and the function of injured neural tracts. DTT seems a better tool than the ROI method on DTI to locate partial injury in a neural tract in an individual patient, because DTT can evaluate the entire neural tract. Limitations of DTT should be considered, although the reconstruction methods of various neural tracts have been well defined, and high repeatability and reliability of these methods have been demonstrated [6, 24, 50, 105–111, 113, 115, 116, 118, 119]. Further studies of the diagnostic criteria for TAI with sensitivity, specificity, and reliability in mild TBI should be encouraged.

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