Central Pain Due to Traumatic Axonal Injury of the Spinothalamic Tract in Patients with Mild Traumatic Brain Injury

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Highlights

• Central pain, a neuropathic pain caused by an injury or dysfunction of the central nervous system, is a common, annoying sequela of mild traumatic brain injury (mTBI).

• The introduction of diffusion tensor imaging allowed assessment of the association of the central pain and injury of the spinothalamic tract (STT), and traumatic axonal injury (TAI) in mTBI.

• The diagnostic approach for TAI of the STT in individual patients with mTBI is discussed, centering around the methods that these studies employed to demonstrate TAI of the STT.
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ABSTRACT

Central pain, a neuropathic pain caused by an injury or dysfunction of the central nervous system, is a common, annoying sequela of mild traumatic brain injury (mTBI). Clarification of the pathogenetic mechanism of central pain is mandatory for precise diagnosis, proper management, and prognosis prediction. The introduction of diffusion tensor imaging allowed assessment of the association of the central pain and injury of the spinothalamic tract (STT), and traumatic axonal injury (TAI) in mTBI. In this review, 6 diffusion tensor tractography studies on central pain due to TAI of the STT in patients with mTBI are reviewed. The diagnostic approach for TAI of the STT in individual patients with mTBI is discussed, centering around the methods that these studies employed to demonstrate TAI of the STT.

Keywords: Diffusion Tensor Imaging; Pain; Spinothalamic Tracts; Traumatic Brain Injury; Cerebral Concussion

INTRODUCTION

Traumatic brain injury (TBI), a major cause of disability, is classified as mild, moderate, and severe based on the severity; 70%-90% patients with TBI are classified with mild TBI (mTBI) [1-4]. Pain is a common sequela in patients with TBI: the prevalence of chronic pain is greater than 50% in patients with TBI, with a higher rate in patients with mTBI, up to 75% [5,6]. While the pathogenetic etiologies of pain include musculoskeletal, vascular, neurogenic, visceral, and iatrogenic mechanisms in TBI, central pain is caused by a lesion or dysfunction of the central nervous system [7-10]. Central pain is a common sequela in patients with TBI: Ofek and Defrin [9] reported 48% of patients with chronic pain following TBI showed central pain in 2007, and Kim et al. [11] reported 69% of patients with mTBI revealed central pain in 2015.

Clarification of the pathogenetic mechanism of central pain is mandatory for precise diagnosis, proper management and prognostic prediction of central pain, but this has yet to be adequately addressed [10-21]. Several theories on the pathogenesis of central pain following brain injury have been proposed: central sensitization, changes in neuronal excitability by disinhibition, alteration in function of the spinothalamic tract (STT), thalamic changes, and inflammation of an involved neural tract [10,11,13,14,16,17]. Several neural structures, including the STT, medial lemniscus, thalamus, periaqueductal gray and cerebral...
cortex, have been suggested as involved in pathogenesis of central pain following brain injury [10,12,13,16,21]. However, after introduction of diffusion tensor imaging (DTI), many studies demonstrated an association of central pain and injury of the STT in pathogenesis of central pain in patients with brain injury, including stroke, multiple sclerosis and TBI [11,18-20,22-30]. Among the above studies in TBI, most focused on central pain due to traumatic axonal injury (TAI), meaning injury of axons due to indirect shearing forces to brain, of the STT in patients with mTBI [11,26-30].

In this chapter, DTI studies on central pain due to TAI of the STT in patients with mTBI are reviewed. Relevant studies were identified using electronic databases (PubMed, Google Scholar, and MEDLINE) from 1966 to 2018. The following key words were used: DTI, diffusion tensor tractography (DTT), central pain, STT, brain injury, cerebral concussion, mTBI, TBI, TAI, and head trauma. This chapter was limited to studies of humans with mTBI. Finally, 6 studies were selected and discussed [11,26-30].

**DTT STUDIES ON TAI IN PATIENTS WITH CENTRAL PAIN FOLLOWING MTBI**

Accurate evaluation of the STT has been difficult using conventional brain imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI). However, DTT provides 3-dimensional visualization and estimation of the STT [31]. Although high prevalence of central pain is reported in patients with TBI, research on this topic has been neglected, especially in mTBI [5,6,9,11,27]. To the best of our knowledge, only 6 studies using DTT have reported on central pain due to TAI of the STT in patients with mTBI (Table 1) [11,26-30].

In 2014, Seo and Jang [26] reported on a patient who showed injury of the STT following mTBI. A 29-year-old male patient suffered head trauma (acceleration and deceleration injury) resulting from a pedestrian car accident. He experienced a dazed feeling for approximately 5 seconds at the time of head trauma without loss of consciousness (LOC) and posttraumatic amnesia (PTA). Glasgow Coma Scale (GCS) score was 15. He began to feel pain at his right shoulder 4 to 5 days after the accident and felt severe pain in multiple areas, including the right chest, the posterior head and neck, both areas of the upper back, and the right arm and leg 2 to 3 weeks after the accident. He was diagnosed as having a herniated cervical disc and internal lumbar disc disruption at the orthopedic surgery department of a university hospital. He had received a cervical interlaminar epidural steroid injection several times...

**Table 1.** DTI studies on TAI of the STT patients with mTBI

<table>
<thead>
<tr>
<th>Authors</th>
<th>Publication year</th>
<th>Patient No.</th>
<th>TBI mechanism</th>
<th>Duration to DTT</th>
<th>Analysis of DTT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seo and Jang [26]</td>
<td>2014</td>
<td>1</td>
<td>Pedestrian accident</td>
<td>2 yr</td>
<td>FA, MD &amp; tract volume Configuration</td>
</tr>
<tr>
<td>Jang and Kwon [27]</td>
<td>2016</td>
<td>1</td>
<td>Pedestrian accident</td>
<td>1 mon 9 mon</td>
<td>Configuration</td>
</tr>
<tr>
<td>Jang and Lee [28]</td>
<td>2016</td>
<td>2</td>
<td>Pratfall</td>
<td>5 mon 10 mon</td>
<td>Configuration</td>
</tr>
<tr>
<td>Jang and Lee [29]</td>
<td>2016</td>
<td>1</td>
<td>Falling object</td>
<td>10 wk</td>
<td>Configuration</td>
</tr>
</tbody>
</table>

DTT, diffusion tensor tractography; TAI, traumatic axonal injury; STT, spinothalamic tract; mTBI, mild traumatic brain injury; TBI, traumatic brain injury; FA, fractional anisotropy; MD, mean diffusivity.
and was prescribed opioid analgesics for approximately 15 months. However, his pain did not improve. When he was admitted to the rehabilitation department of another university hospital 2 years after the accident, he complained of pain on the posterior head and neck, both upper trapezius and subscapular areas, and the right arm and leg. The characteristics and severity of pain were as follows: throbbing pain in both subscapular areas, characterized by allodynia and hyperalgesia (visual analogue scale [VAS] score: 6–7) [32], constant tingling and throbbing sensation in the posterior neck region with a lancinating sensation in both upper trapezius areas (VAS score: 6), numbness and throbbing sensation on the posterior head (VAS score: 5), tingling sensation on the right lateral leg (VAS score: 5) with a sharp lancinating pain in the right sole (VAS score: 7), and a constant burning sensation in the right hand and migrating shooting pain in the medial forearm (VAS score: 6) [10,32-36]. Myofascial pain syndrome or fibromyalgia were ruled out by physical examination. Any abnormality was not detected on conventional brain MRI electromyography study. In addition, no abnormality was observed on cervical, thoracic, and lumbar spine MRI. On 2-year DTT, the STTs of both hemispheres were thinner than those of normal control subjects. The FA values of the right and left STT were more than 2 standard deviations higher and lower than those of normal control subjects, respectively. The tract volume of the right STT was more than 2 standard deviations lower than that of normal control subjects. The reliability tests showed good intra-analyzer (intraclass correlation coefficient [ICC] = 0.96 to 0.99) and inter-analyzer (ICC = 0.93 to 0.95) reliability. The authors assumed that some portion of the pain in the trunk and extremities in this patient was ascribed to central pain caused by injury of both STTs [26].

In 2015, Kim et al. [11] demonstrated a relation between injury of the STT and chronic central pain in patients with mTBI. The authors recruited forty patients with mTBI who were admitted to the rehabilitation department of a university hospital and 21 normal control subjects. The authors excluded 8 patients with other pathologies: brain lesion using conventional brain MRI, radiculopathy or peripheral neuropathy using electromyography and nerve conduction study, and myelopathy using spinal MRI or central motor conduction time. Among 32 patients, 22 patients (69%) had central pain with the characteristics of neuropathic pain, characterized by stimulation-independent pain: shooting, lancinating, burning, electric shock-like sensation, and paresthesia (crawling, itching, tingling sensation); stimulus evoked pain: hyperalgesia or allodynia [10,33-36]. The patients with central pain showed decreased FA and tract volume, and increased MD of the STTs compared with the patients without central pain and normal subjects, indicating injury of the STT. Therefore, the authors concluded that injury of the STT was related to central pain in patients with mTBI and injury of the STT appeared to be a pathogenetic etiology of central pain following mTBI [11]. Although this study reported high risk of central pain in mTBI, a possible design flaw is that patients with severe clinical manifestations were included in this study compared to all patients with mTBI because the authors recruited from among rehabilitation admissions.

Jang and Kwon [27] reported on degeneration of an injured STT in a patient with mTBI in 2016. A 56-year-old female suffered head trauma resulting from a pedestrian car accident: the patient's head hit the ground after falling down after being struck by a car. The patient did not experience LOC and PTA. When she was transferred to a university hospital after the car accident, her GCS score was 15. She began to feel pain in her left hand and foot about 7 days after onset. The characteristics and severity of pain were as follows: constant tingling and pricking sensation without allodynia or hyperalgesia (VAS score: 3–4) [10,32-34,36]. No specific abnormality was observed on brain and spine MRI, and an electromyography study. She was prescribed gabapentine (300 mg/day) one month after onset and her pain
Central Pain Due to TAI of the STT in mTBI

was well-controlled to a tolerable level. At 6 months after onset, the central pain in the left hand and foot became aggravated, with a VAS score 6 [32]. Therefore, 8 months after onset, the total dose of gabapentine was increased to 600 mg/day and the pain was well-controlled to a tolerable state. Partial tearing in both STTs was observed on 1-month DTT. By contrast, both partially torn STTs had become thinner on 9-month DTT. The authors concluded that degeneration of injured STTs was demonstrated in this patient [27].

In 2016, Jang and Lee [28] reported on 2 patients who revealed central pain due to injury of the STT caused by indirect head trauma following a pratfall. Patient 1 was a 21-year-old right-handed female who had suffered a pratfall on a wet floor while working at a company, with no history of direct head trauma. The patient experienced LOC for approximately 10 minutes and PTA for approximately 30 minutes at the time of head trauma, and her GCS was 15 when she arrived at the hospital. She had begun to feel pain in both upper trunk and lower back, and the left leg since about 5 days after onset. The characteristics and severity of pain were as follows: constant tingling and throbbing sensation with allodynia (VAS score: 7) [10,32-36].

Patient 2 was a 39-year-old right-handed male who had suffered a pratfall on a wet floor while walking without direct head trauma. The patient did not experience LOC or PTA at the time of head trauma, and his GCS was 15 when he arrived at the hospital. He began to feel pain in both arms and legs about 4 days after the pratfall with the following characteristics of pain: constant tingling and pricking sensation without allodynia or hyperalgesia (VAS score: 8) [12]. On DTT of patient 1, partial tearing of the subcortical white matter was observed in the right STT. On DTT of patient 2, the right STT showed partial tearing at the subcortical white matter and the left STT revealed partial thinning. The authors excluded other pathologies using conventional brain MRI, spine MRI, electromyography study, and previous history. The authors suggested that minor indirect head trauma can also cause TAI of the brain [28].

During the same year, Jang and Seo [29] reported on a patient with central pain due to injury of the STT after suffering head trauma by a falling object in 2016. While seated in a subway car, a falling large box (100 × 30 × 30 cm) hit the vertex of her head. The patient experienced LOC for approximately 2 minutes and PTA for approximately 5 minutes with GCS score of 15. She began to feel severe bursting pain in her head, neck and upper back immediately after the head trauma. Furthermore, she began to feel pricking pain in her left arm and leg approximately 3 hours after the head trauma. Although she visited several hospitals to find the cause of her pain, she could not get a specific diagnosis. Ten months after the injury, she visited the rehabilitation department of a university hospital. She complained of constant pain with hyperalgesia in her head, left arm and leg. The characteristics and severity of pain were as follows; 1) head: pricking sensation (VAS score: 5–7), 2) left arm: pricking and squeezing (VAS score: 3–7), and 3) left leg: bursting sensation (VAS score: 6–7) [10,32-36].

No specific focal lesion was observed on brain and spine MRI, and an electromyography study revealed no evidence of peripheral neuropathy or radiculopathy. On the 10-month DTT, partial tearing and narrowing were observed in the STTs in both hemispheres. She was prescribed gabapentine (900 mg/day) for one month, and her pain was well-controlled to a tolerable level. Her physicians concluded that the cause of central pain in this patient and TAI was the most likely pathogenetic mechanism for the STT injuries [29].

Jang and Lee [30] reported on a patient with mTBI with TAI of the STT following whiplash injury in 2017. This 26-year-old female patient suffered from indirect head trauma resulting from whiplash injury after being hit from behind by a slowly moving car. At the time of head trauma, she felt a tingling sensation in all extremities although she did not experience LOC.
Five days after onset, she began to experience tremor on the right leg and subsequently tremor developed in the left leg. At 8 days after onset, she began to feel a tingling sensation on both legs. The neuropathic pain was aggravated with passage of time. On 10-week DTT, the tiny fibers of the dentatorubrothalamic tract were reconstructed only at the brainstem level and the STT was thin in both hemispheres. By contrast, the corticospinal tract and corticoreticulospinal tract showed partial tearing and discontinuation at the subcortical white matter level in both hemispheres. The authors concluded that severe and extensive TAI of various neural tracts including the STT was demonstrated in a patient with mTBI following whiplash injury [30].

**DIAGNOSTIC APPROACH OF TAI OF THE STT IN PATIENTS WITH CENTRAL PAIN FOLLOWING MTBI**

There are more than 40 recent papers that reported TAI in individual patients with mTBI using DTT [20,21,26-30,37-65]. Among these, 5 reported on TAI of the STT in individual patients with mTBI [26-30]. The methods to demonstrate TAI of the STT of 5 studies can be summarized as follows [66] (Supplementary Fig. 1). First, head trauma history compatible with mTBI is required. According to the definition of mTBI from the American Congress of Rehabilitation Medicine, the patient must have a head trauma history with 3 conditions of mTBI in terms of LOC, PTA, and GCS. If a patient did not suffer LOC, any alteration in mental state (feeling dazed, disoriented, or confused) at the time of the accident is necessary [66]. Second, development of neuropathic pain characterized by stimulation-independent pain: shooting, lancinating, burning, electric shock-like sensation, and paresthesia (crawling, itching, tingling sensation); stimulus evoked pain: hyperalgesia or allodynia after head trauma that is never observed before the head trauma [10,11,33,34,36,66]. The possibility of delayed onset of the central pain due to secondary axonal injury 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 STT should also be considered [26-28,66-68]. Third, evidence of TAI of the STT on DTT is required [11,26-30]. TAI of the STT 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 the STT [66] (Fig. 1). Fourth, the abnormality of DTT by previous head trauma, neurological disease, aging or artifact of DTT should be ruled out [66]. Fifth, peripheral nerve injury, spinal cord injury, and musculoskeletal problems should be ruled out.

**Fig. 1.** Configurational analysis of the STT in patients with mTBI (reprinted from reference 66).

STT, spinothalamic tract; mTBI, mild traumatic brain injury.
through other studies such as electromyography study, radiological study or ultrasonography [66]. Improvement of the central pain with management for the central pain could be an additional evidence for TAI [66]. For example, when a patient develops central pain due to injury of the STT following mTBI, if the patient’s pain improves with the administration of specific drugs for central pain such as gabapentine, that would be 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 occur in multiple neural tracts following diffuse head trauma like mTBI [30,53,55,66].

**CONCLUSION**

In this chapter, 6 DTT studies on central pain due to TAI of the STT in patients with mTBI were reviewed along with the definition and history of TAI in mTBI. While considering the methods that these studies employed to diagnosis TAI of the STT, the diagnostic approach for TAI of the STT in individual patients with mTBI was summarized. Fewer studies with small number of patients on this topic have been reported compared with the studies on other topics in patients with mTBI. In addition, all studies focused to demonstrate TAI in patients with central pain following mTBI. Therefore, conduct of further studies on this topic, particularly involving a large number of subjects, clinical characteristics which are different with other TBI and other brain pathologies, the diagnostic criteria for TAI with sensitivity, specificity and reliability, therapeutic and preventive strategies, and prognosis should be encouraged.

**SUPPLEMENTARY MATERIAL**

**Supplementary Fig. 1**

Diagnostic approach of TAI of the STT in patients with central pain following mTBI (reprinted with modification from reference 66).

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