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Relation between injury of the periaqueductal gray and central pain in patients with mild traumatic brain injury

Observational study

Sung Ho Jang (MD), So Min Park (MD), Hyeok Gyu Kwon (PhD)*

Abstract

The periaqueductal gray (PAG) plays a pivotal role in pain modulation. We attempted to examine the relation between injury of the PAG and central pain in patients with mild traumatic brain injury (TBI).

Sixty-one patients with mild TBI with central pain and 31 healthy control subjects were recruited for this study. Visual analog scale (VAS) was used for evaluation of central pain. The region of interest was defined for the PAG and the fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were measured.

The FA value was significantly lower in the patient group than in the control group ($P < 0.05$). However, no significant difference in the ADC value was observed between the patient and control groups ($P > 0.05$). VAS score of the patient group showed significant moderate negative correlation with the FA ($r = -0.38$), while no significant correlation was observed between VAS score and the ADC value ($P < 0.05$).

We demonstrated injury of the PAG in patients with central pain following mild TBI and the degree of injury of the PAG was closely related to the degree of central pain.

Abbreviations: ADC = apparent diffusion coefficient, DTI = diffusion tensor imaging, FA = fractional anisotropy, PAG = periaqueductal gray, TBI = traumatic brain injury, VAS = visual analog scale.

Keywords: central pain, diffusion tensor imaging, mild traumatic brain injury, periaqueductal gray

1. Introduction

Central pain, which is caused by head trauma, spinal cord injury, stroke, tumor, and so on, is ascribed to an injury or malfunction of the central nervous system and presents the characteristics of neuropathic pain.[1–3] Regarding traumatic brain injury (TBI), it has been reported that approximately 48% to 68% of patients with TBI have experienced central pain.[3,4] As a result, understanding of the pathogenetic mechanism for central pain is clinically important. However, knowledge on this topic is limited because various brain structures including thalamus, dorsolateral prefrontal cortex, periaqueductal gray (PAG) are known to be involved in the pathogenesis of the central pain.[5–9] Among the above-mentioned brain structures, the PAG is known to play a pivotal role in pain modulation.[10–12] The PAG is approximately 14 mm long and 4 to 6 mm wide, and encircles the cerebral aqueduct at the tegmentum of the midbrain where is known to be vulnerable to TBI.[12–14] It is known to be a main descending pain inhibitory system as well as involving the visceral defense reactions, fear, anxiety, cardiorespiratory control, and depression.[10–12,15–17] Many studies have reported that injury of the PAG was related to central pain.[8,18–20] However, no study in patients with central pain following mild TBI has been reported so far.

TBI is a major cause of mortality and disability.[21] On the basis of severity, it is classified as mild, moderate, or severe and 70% to 90% of cases of TBI are mild TBI.[22] One feature of mild TBI is no specific lesion on conventional magnetic resonance imaging (MRI); hence, demonstration of neural injury in mild TBI was limited.[23] However, recent development of diffusion tensor imaging (DTI) has enabled quantitative estimation of subcortical brain structures in the human brain[24] and many studies have demonstrated injury of various brain structures including the corticospinal tract, spinothalamic tract, cingulum, and cortico-reticular pathway in patients with mild TBI.[4,25,26] However, no study on injury of the PAG has been reported so far. We hypothesized that injury of the PAG might be associated with the central pain.

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In the current study, using DTI, we attempted to examine the relation between injury of the PAG and central pain in patients with mild TBI.

2. Methods

2.1. Subjects

Sixty-one patients (male: 28, female: 33, mean age: 45.7 [12.9] years, range: 20–69 years) with TBI and 31 healthy control subjects (male: 16, female: 15, mean age: 43.6 [11.3] years, range: 22–64 years) with no history of neurological, physical, or psychiatric illness were recruited for this study. Inclusion criteria for patients were as follows: loss of consciousness for <30 min, post-traumatic amnesia for ≤24 h, and initial Glasgow Coma Scale score of 13 to 15,[27] and no specific lesion was observed on brain MRI (T1-weighted, T2-weighted, and Fluid attenuated inversion recovery images); more than 1 month after onset of TBI; age at the time of head trauma: ≥20 years old; presence of central pain after the onset of head trauma presenting the characteristics of neuropathic pain: stimulation-independent pain: shooting, lancinating, burning, electric shock-like sensation, and paraesthesia (crawling, itching, tingling sensation); stimulus evoked pain: hyperalgesia or allodynia by environmental stimuli[9,28–30]; no radiculopathy or peripheral neuropathy on electromyography and nerve conduction study; no musculoskeletal problem (e.g., myofascial pain syndrome, complex regional pain syndrome, heterotopic ossification); and no history of previous head trauma, neurologic or psychiatric disease. This study was conducted retrospectively and the study protocol was approved by the Institutional Review Board of a Yeungnam University Hospital.

Table 1

Demographic and clinical data of the patient and control groups.

	Patient group	Control group
Mean age, y	45.7 (12.9)	43.6 (11.3)
Sex, male:female	28:33	16:15
LOC/PTA, min	5.7 (8.8)/11.1 (23.8)	
GCS score	14.8 (0.5)	
VAS score	6.0 (1.59)	
Location of central pain		
Head or neck	47	
Upper extremity	34	
Trunk	17	
Lower extremity	32	
Mechanism of injury		
Motor vehicle accident	41	
Pedestrian accident	7	
Fall down	7	
Bicycle accident	4	
Hit by falling object	2	
ICHD-3		
Acute headache attributed to mild traumatic injury to the head	5	
Persistent headache attributed to mild traumatic injury to the head	23	
Acute headache attributed to whiplash	3	
Persistent headache attributed to whiplash	16	
No head or neck pain	14	
Mean duration to DTI, mo	6.8 (5.8)	

Values represent mean (±standard deviation).

DTI = diffusion tensor imaging, GCS = Glasgow Coma Scale, ICHD = The International Classification of Headache Disorders, LOC = loss of consciousness, PTA = post-traumatic amnesia, VAS = visual analog scale.

2.2. Clinical evaluation

Central pain of patients was evaluated using the visual analog scale (VAS) and the highest score of the VAS was selected. The reliability and validity of the VAS is well-established.[31] In addition, central pain was classified according to International Classification of Headache Disorders.

2.3. Diffusion tensor imaging

A 6-channel head coil on a 1.5T Philips Gyroscan Intera (Philips, Ltd, Best, The Netherlands) with single-shot echo-planar imaging was used for acquisition of DTI data. For each of the 32 diffusion-sensitizing gradients, 70 contiguous slices were acquired parallel to the anterior commissure–posterior commissure line. Imaging parameters of DTI were as follows: acquisition matrix = 96×96; reconstructed to matrix = 192×192; field of view = 240×240 mm^2; repetition time = 10,398 ms; echo time = 72 ms; parallel imaging reduction factor = 2; echo-planar imaging factor = 59; b = 1000 s/mm^2; number of excitations = 1; and a slice thickness of 2.5 mm. Eddy current-induced image distortions were removed using affine multiscale 2-dimensional registration at the Oxford Centre for Functional Magnetic Resonance Imaging of Brain Software Library (FSL; www.fmrib.ox.ac.uk/fsl). DTI-Studio software (CMRM, Johns Hopkins Medical Institute, Baltimore, MD) was used for evaluation of the PAG.[32] For selection of region of interest, size of the PAG (known anatomical size of PAG are 4–6 mm) was measured at the midbrain level on T2-weighted brain MR images in order to find the boundary of the PAG and then based on the cerebral aqueduct, the same size of the PAG for each subject was applied to a b0 map of DTI at the midbrain level for measurement of the fractional anisotropy (FA) and apparent diffusion coefficient (ADC).[12–14] The average width and length of PAG was 4.32 (0.57) mm and 4.53 (0.65) mm in the patient group and 4.38 (0.56) mm and 4.61 (0.71) mm in the control group.

2.4. Statistical analysis

SPSS software (v.15.0; SPSS, Chicago, IL) was used for data analysis. An independent *t* test was used for determination of differences in the values of FA and ADC between the patient and control groups. Using Pearson correlation, VAS score was used in determination of correlation with the FA and ADC. The significant level of the *P* value was set at 0.05.

3. Results

The demographic, clinical, and DTI parameter data for patient and control groups are summarized in Table 1. Average of loss of consciousness, post-traumatic amnesia, Glasgow Coma Scale, and VAS was 5.7 (8.8) min, 11.1 (23.8) min, 14.8 (0.5) score, and 6.0 (1.59) score. According to International Classification of Headache Disorders, 5 patients (8.2%) belonged to "Acute headache attributed to mild traumatic injury to the head," 23 patients (37.7%) to "Persistent headache attributed to mild traumatic injury to the head," 3 patients (4.9%) to "Acute headache attributed to whiplash," and 16 patients (26.2%) to "Persistent headache attributed to whiplash"; however, remaining 14 patients (23.0%) showed no head or neck pain.

The FA value of the patient group was significantly lower than that of the control group ($P < 0.05$) (Fig. 1A). However, no significant difference in the ADC value was observed between the

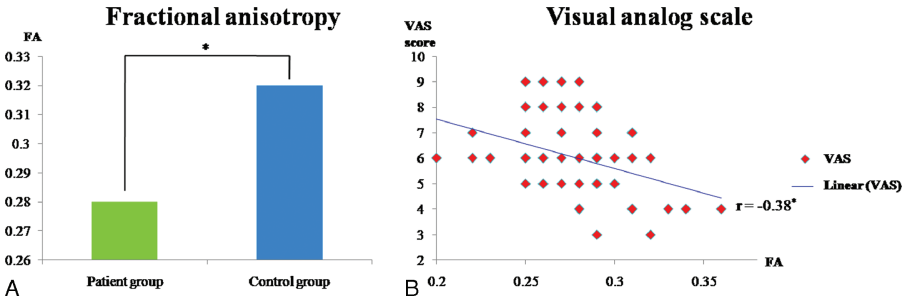

Figure 1. (A) Results of independent *t* test in the FA value between the patient and control groups. The FA value of the patient group is significantly lower than that of the control group. (B) Results of Pearson correlations between VAS and FA value of the patient group. The VAS score shows moderate correlation with the FA value (negative correlation, $r = -0.38$). FA = fractional anisotropy, VAS = visual analog scale. $^{*}P < 0.05$.

patient and control groups ($P > 0.05$). VAS score of the patient group showed significant moderate negative correlation with the FA ($r = -0.38$) ($P < 0.05$) (Fig. 1B), while no significant correlation was observed between VAS score and the ADC value ($P > 0.05$) (Table 2).

4. Discussion

In the current study, using DTI, injury of the PAG was examined in patients with central pain following mild TBI. According to our findings, the FA value in the patient group was lower than that of the control group and showed significant correlations with VAS score (negative correlation, $r = -0.38$) ($P < 0.05$). In the field of DTI, the FA, which is a scalar measure, value means the degree of directionality of water diffusion and has a range of 0 (completely isotropic diffusion) to 1 (completely anisotropic diffusion).[25] In white matter, water diffuses more easily along axons than perpendicular to them, and increased organization of white matter tracks will be reflected in increased FA values. As a result, the FA value is the most commonly used in evaluating the state of brain structures in patients with brain injury and it represents the degree of directionality of microstructures such as axons, myelin, and microtubules.[33] Therefore, significant decrement of the FA value indicates injury of the PAG. The negative correlation of the FA value with the VAS suggests that the degree of PAG in the patient group was related to the degree of central pain. Because the patients did not show any specific lesion on conventional MRI, traumatic axonal injury appeared to be a plausible pathogenetic mechanism for injury of the PAG.[34] In addition, the PAG is located at the midbrain, which is known to be a vulnerable brain structure by traumatic axonal injury.[35] Consequently, the central pain in the patient group appeared to be at least in part ascribed to injury of the PAG. In terms of pain modulation, various brain structures including the PAG, thalamic nuclei, dorsolateral prefrontal cortex, anterior cingulate cortex, and amygdala are involved.[36–39] In detail, the thalamic nuclei receive pain information from periphery and transmit to the cerebral cortex via the spinothalamic tract and it is related to the descending inhibition to modulate nociceptive inputs.[36] The dorsolateral prefrontal cortex and anterior cingulate cortex which is 1 of the key cortical areas are mainly related to modulation of pain perception.[37,38] In addition, the amygdala modulates pain behavior and experiences using inhibiting pain processing[39]; hence, although various brain structures are involved in pain modulation, we focused on injury of the PAG following mild TBI because the PAG is a key role in pain modulation and the PAG which is located at the midbrain can be vulnerable to TBI.[10–12,35]

Since the introduction of DTI, a few studies have suggested that injury of the spinothalamic tract is a pathogenetic mechanism of central pain in patients with mild TBI.[4,40,41] To the best of our knowledge, using DTI, 2 studies reported on abnormality of the PAG in patients with migraine, although no study in patients with mild TBI has been reported so far.[42,43] In 2007, DaSilva et al reported that the FA value in ventrolateral PAG of 12 patients with migraine was lower than that of controls (12 age- and sex-matched healthy subjects).[42] In 2015, Ito et al demonstrated increment of the ADC value without significant change of the FA value in the PAG in 20 patients with episodic migraine compared with that of controls (20 age- and sex-matched healthy subjects).[43] The increment of ADC value that reflects the magnitude of water diffusion in tissue indicated injury of the PAG.[33] Therefore, the results of our study appear to be consistent with those of the above-mentioned previous studies. Consequently, to the best of our knowledge, this is the first study to demonstrate the relation between central pain and injury of the PAG in patients with mild TBI. However, limitations of this study should be mentioned: the technique for measurement of DTI parameters is operator-dependent, particularly defining the region of interest,[44] regarding DTI parameters, because ADC value reflects a specific diffusion coefficient on 1 gradient, mean diffusivity which reflects average diffusion coefficient on 3 gradients [(Dx + Dy + Dz)/3] could be better than ADC value for evaluation of brain, and this study was conducted retrospectively. Therefore, we could not provide the outcome or prognosis of the central pain.

In conclusion, we demonstrated injury of the PAG in patients with central pain following mild TBI and the degree of injury of the PAG was found to be closely related to the degree of central pain. These results suggest that DTI could provide useful information in detecting injury of the PAG, which could not be found on conventional brain MRI in patients with mild TBI. In addition, evaluation of the PAG using DTI would be necessary in patients who complain of central pain following mild TBI.

Table 2

Diffusion tensor imaging parameters of the periaqueductal gray.

	Patient group	Control group	*P*
Fractional anisotropy	0.28 (0.03)	0.32 (0.03)	0.001*
Apparent diffusion coefficient	0.89 (0.06)	0.87 (0.05)	0.255

Values represent mean (±standard deviation).

* Significant differences between patient and control groups, $P < 0.05$.

Further studies on other brain structures related to pain modulation should be encouraged.

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