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Relationship between hyperhidrosis and hypothalamic injury in patients with mild traumatic brain injury

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Abstract

Hyperhidrosis is clinical symptom of various diseases and is an important clinical feature of paroxysmal sympathetic hyperactivity (PSH). Traumatic brain injury (TBI) is known to be most common condition associated with PSH, and PSH has been mainly reported in moderate and severe TBI. However, very little has been reported on PSH or hyperhidrosis in mild TBI patients. In this study, we used diffusion tensor imaging (DTI) to investigate the relationship between hyperhidrosis and hypothalamic injury in patients with mild TBI. Seven patients with hyperhidrosis after mild TBI and 21 healthy control subjects were recruited for this study. The Hyperhidrosis Disease Severity Scale was used for evaluation of sweating at the time of DTI scanning. The fractional anisotropy and apparent diffusion coefficient DTI parameters were measured in the hypothalamus. In the patient group, the fractional anisotropy values for both sides of the hypothalamus were significantly lower than those of the control group ($P < .05$). By contrast, the apparent diffusion coefficient values for both sides of the hypothalamus were significantly higher in the patient group than in the control group ($P < .05$). In conclusion, we detected hypothalamic injuries in patients who showed hyperhidrosis after mild TBI. Based on the results, it appears that hyperhidrosis in patients with mild TBI is related to hypothalamic injury.

Abbreviations: ADC = apparent diffusion coefficient, DTI = diffusion tensor imaging, FA = fractional anisotropy, HDSS = Hyperhidrosis Disease Severity Scale, PSH = paroxysmal sympathetic hyperactivity, TBI = traumatic brain injury

Key Words: diffusion tensor imaging, hyperhidrosis, hypothalamus, mild traumatic brain injury, paroxysmal sympathetic hyperactivity.

1. Introduction

Hyperhidrosis is a condition characterized by abnormally increased sweating, that is, sweating in excess of that required for the regulation of body temperature.[1] Hyperhidrosis can deteriorate a subject's quality of life from psychological, emotional, and social perspectives.[2] Although hyperhidrosis is clinical symptom of various diseases, it is an important clinical feature of paroxysmal sympathetic hyperactivity (PSH), a syndrome that causes episodes of increased sympathetic nervous system activity in patients with an acquired brain injury.[3,4] While PSH can arise from many types of acquired brain injury, traumatic brain injury (TBI) is reported to be the most common disease associated with PSH, and PSH has been mainly reported in patients with moderate and severe TBI.[4–8] However, very little has been reported about PSH or hyperhidrosis in patients with mild TBI.[9]

The central regulatory center for thermoregulatory sweating is located in the hypothalamus,[10,11] and hypothalamic injury has been suggested as an important pathophysiological mechanism associated with hyperhidrosis in patients with brain injuries.[12–18] Precise evaluation of the hypothalamus in the live human brain has been limited due to its anatomical characteristics: very small size and deep location within the white matter.[19,20] Nonetheless, diffusion tensor imaging (DTI) allows evaluation of the hypothalamus in the live human brain. By examining various DTI parameters, several studies have used DTI to report on the relationship between hypothalamic injury and various clinical features, including narcolepsy, depression, and cognitive fatigue, exhibited in various brain diseases including TBI, hypoxic-ischemic brain injury, and multiple sclerosis.[21–27] However, no study on the relationship between hyperhidrosis and hypothalamic injury has been reported.

In this study, by using DTI, we investigated the relationship between hyperhidrosis and hypothalamic injury in patients with mild TBI.

2. Methods

2.1. Subjects

Fourteen patients (male: 4, female: 10, mean age: 52.5 ± 6.7 years, range: 39–60 years) with mild TBI and 21 age- and

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sex-matched healthy control subjects (male: 7, female: 14, mean age: 48.1 ± 9.8 years, range: 35–60 years) with no previous history of neurological, physical, or psychiatric illness were recruited for this study (Table 1). The following inclusion criteria were used in the recruitment of patients: (1) loss of consciousness for < 30 minutes, posttraumatic amnesia for ≤ 24 hours, and initial Glasgow Coma Scale score of 13–15;[28] (2) no specific lesion observed on brain MRI (T1-weighted, T2-weighted, and fluid-attenuated inversion recovery images); (3) more than 1 month elapsed since onset of TBI; (4) presence of hyperhidrosis (n = 7) and no presence of hyperhidrosis (n = 7) after the onset of head trauma; and (5) no history of previous head trauma and neurologic or psychiatric disease. All healthy subjects understood the purpose of the study and provided written, informed consent prior to participation. This study was conducted retrospectively, and the study protocol was approved by the institutional review board of a university hospital.

2.2. Clinical evaluation

The previously developed Hyperhidrosis Disease Severity Scale (HDSS) was used to evaluate the subjects' sweating characteristics at the time of DTI scanning. The HDSS score ranged from 1 to 4 with score = 1 signifying that sweating is never noticeable and never interferes with daily activities, score 2 indicating that sweating is tolerable but sometimes interferes with daily activities, score 3 indicating that sweating is barely tolerable and frequently interferes with daily activities; and score 4 signifying that sweating is intolerable and always interferes with daily activities.[29] The patients were classified according to presence of hyperhidrosis: group A; patients with hyperhidrosis, group B; patients without hyperhidrosis. The average HDSS score in the patient group was 2.4 ± 0.8 (Table 1). Clinical features of PSH present in each patient and the HDSS scores for each patient are presented in Table 2.

2.3. Diffusion tensor imaging

A multichannel head coil on a 1.5 T Philips Gyroscan Intera (Philips, Ltd, Best, Netherlands) with 32 gradients was used for acquisition of DTI data. DTI imaging parameters were set as follows: acquisition matrix = 96 × 96; reconstructed to matrix = 192 × 192; field of view = 240 mm × 240 mm; repetition time = 10,398 ms; echo time = 72 ms; parallel imaging reduction factor = 2; echo-planar imaging factor = 59; b = 1000s/mm^2; number of excitations = 1; and slice thickness = 2.5 mm. Eddy current-induced image distortions were removed using affine multi-scale 2-dimensional registration as provided by the Oxford Centre for Functional Magnetic Resonance Imaging of Brain Software Library. DTI-Studio software (CMRM, Johns Hopkins Medical Institute, Baltimore, MD, USA) was used for evaluation of the hypothalamus, which was identified by establishing the optic tract as the anterior boundary and the mammillary body as the posterior boundary at the level of the upper midbrain (Fig. 1).[23,30] The fractional anisotropy (FA) and apparent diffusion coefficient (ADC) values were measured in the area identified as the hypothalamus.[31]

2.4. Statistical analysis

Statistical analyses were performed using SPSS software (v. 25.0; SPSS, Chicago, IL, USA). One-way analysis of variance(ANOVA) was performed for determination of differences in the FA and ADC values between the 3 groups. When a significant difference was detected between the 3 groups, Bonferroni post hoc test was performed for determination of the differences in FA and ADC values between the 3 groups. The significance level for the obtained P value was set at .05.

3. Results

A summary of the DTI parameter results for the hypothalamus in the patient and control groups is shown in Table 3. In the group A, the FA values for both sides of the hypothalamus were significantly lower than those of the group B and control group (P < .05). By contrast, the ADC values for both sides of the hypothalamus were significantly higher in the group A than in the group B and control group (P < .05). No significant differences in FA and ADC values between the group B and control group (P < .05).

4. Discussion

In the current study, by using DTI hypothalamic injuries were investigated in patients exhibiting hyperhidrosis following mild TBI. Our results are summarized as follows: (1) the group A had lower FA values and higher ADC values for both sides of the hypothalamus than those of the group B and control group (P < .05); and (2) all patients of group A exhibited a HDSS score of 2 or greater. The FA and ADC values are commonly used to demonstrate the status of brain structures in patients with brain injuries. The FA value indicates the degree of directionality of water diffusion; consequently, it reflects fiber density, axonal diameter, and white matter myelination, whereas the ADC value indicates the magnitude of water diffusion.[32] Therefore, a low FA value combined with a high ADC value is indicative of brain injury.[33] In the present study, the FA and ADC values indicate

Table 1

Demographic data for the patient and control groups.

		Group A	Group B	Control group
Sex (male:female)		2:5	2:5	7:14
Mean age, years		51.4 (6.7)	53.6 (6.5)	48.1 (9.8)
LOC, minutes		8.1 (11.3)	5.0 (10.3)	–
PTA, minutes		10.6 (22.1)	10.0 (12.8)	–
GCS score		14.9 (0.4)	14.7 (0.7)	–
HDSS score		2.4 (0.8)	-	–
Mechanism of injury	Motor vehicle accident	7	7	–
Mean duration to DTI (months)		13.6 (5.8)	17.0 (6.9)	–

Values are mean (± standard deviation).
DTI = diffusion tensor imaging, GCS = Glasgow Coma Scale, HDSS = Hyperhidrosis Disease Severity Scale, LOC = loss of consciousness, PTA = posttraumatic amnesia.

Table 2

Severity of hyperhidrosis and presence of clinical features of paroxysmal sympathetic hyperactivity in the individual patients.

	HDSS	Fever	Tachycardia	Hypertension	Tachypnea	Dystonia
Patient 1	2	–	–	–	–	–
Patient 2	4	–	–	+	–	–
Patient 3	3	–	–	–	+	–
Patient 4	2	–	–	+	–	–
Patient 5	2	–	–	+	–	–
Patient 6	2	–	–	–	–	–
Patient 7	2	–	–	–	–	–

Score 1: sweating is never noticeable and never interferes with daily activities, score 2: sweating is tolerable but sometimes interferes with daily activities, score 3: sweating is barely tolerable and frequently interferes with daily activities, and score 4: sweating is intolerable and always interferes with daily activities.
HDSS = Hyperhidrosis Disease Severity Scale.

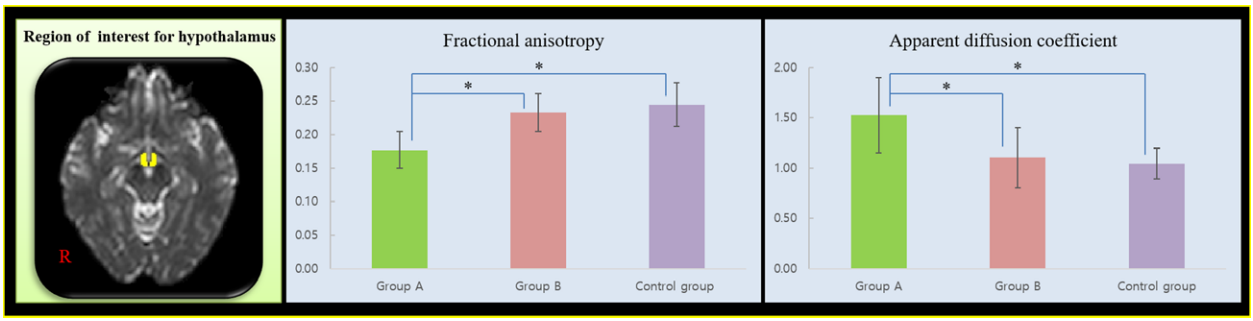

Figure 1. Region of interest for the hypothalamus and results of comparison of the fractional anisotropy and apparent diffusion coefficient values between 3 groups. *$P < .05$.

Table 3

Diffusion tensor imaging parameters of the hypothalamus in the 3 groups.

	Fractional anisotropy		Apparent diffusion coefficient	
	Right	Left	Right	Left
Group A	0.19 (0.02)*	0.18 (0.03)*	1.45 (0.39)*	1.53 (0.38)*
Group B	0.23 (0.02)	0.23 (0.03)	1.07 (0.02)	1.14 (0.34)
Control group	0.25 (0.03)	0.24 (0.03)	1.04 (0.15)	1.05 (0.16)

Values represent mean (±standard deviation)
*$P < .05$ for comparison between the group A and group B and between group A and control group.

the presence of hypothalamic injuries in the group A and these injuries might be related to the concurrent presence of hyperhidrosis in the group A.

Hyperhidrosis is a clinical feature of PSH,[3,4] and PSH presence is determined, in the absence of other potential causes such as uncontrolled sepsis or airway obstruction, by the transient presence of 4 of the following 6 criteria: fever, tachycardia (heart rate > 120 beats/min or > 100 beats/min if treated with a beta-blocker), hypertension (systolic blood pressure > 160 mm Hg or pulse pressure > 80 mm Hg), tachypnea (respiratory rate > 30 breaths/min), hyperhidrosis, and extensor posturing or severe dystonia.[3,4] Although the pathophysiological mechanisms of PSH have not clearly elucidated, 2 main mechanisms have been suggested: (1) simple disconnection of cortical inhibitory centers such as the insula and cingulate cortex to the brain areas responsible for supraspinal control of sympathetic tone (hypothalamus, diencephalon, and brainstem); and (2) the excitatory: inhibitory ratio model in which paroxysms are driven by abnormal processing of afferent stimuli within the spinal cord following disconnection of descending inhibitory pathways.[7,9,12,34] Although no patient in this study satisfied the diagnostic criteria for PSH, we suggest that the hyperhidrosis exhibited by our patients may be considered a clinical feature indicative of PSH because the hypothalamus is an important area for the development of PSH.[7,12,34] We assume that the reason our patients could not meet the diagnostic criteria of PSH is related to their head injuries being milder than that of moderate and severe TBI.

The hypothalamus has been regarded as a key regulator of thermoregulatory sweating.[10,11] Several studies have reported associations between hypothalamic injury and hyperhidrosis in patients with brain injury, including those with cerebral infarct and multiple sclerosis.[15–18] Smith (2001) reported that hyperhidrosis was ascribed by hypothalamic stroke.[16] In 2007, Alan et al reported hypothalamic dysfunction was affect the hyperhidrosis as a side effect of deep brain stimulation.[15] Therefore, the results of our study appear to be consistent with those of the abovementioned studies.[15–18] To the best of our knowledge, this is the first study to demonstrate an association between hyperhidrosis and hypothalamic injury in patients with mild TBI. However, limitations of this study should be considered. First, the technique for measurement of DTI parameters is operator-dependent, particularly during the definition of the region of interest; regardless, we attempted to define consistently the hypothalamus by using definite boundaries in this study.[35] Second, a small number of subjects were recruited in this study. Third, although HDSS is quick and easy self-rated evaluation method, it cannot be applied to the patients with a cognitive problem. Therefore, conduct of further prospective studies that enroll larger numbers of subjects should be encouraged.

In conclusion, by using DTI, we detected hypothalamic injury in patients who showed hyperhidrosis after mild TBI. Based on the results, it appears that hyperhidrosis exhibited by patients with mild TBI can be related to hypothalamic injury. Our results suggest that DTI could be useful in detecting hypothalamic injury, injuries that may not be detected on conventional brain MRI in patients with mild TBI.

Author contributions

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