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

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**Abstract**

Hyperhidrosis is a condition characterized by abnormally increased sweating, that is, sweating in excess of that required for the regulation of body temperature. Hyperhidrosis can deteriorate a subject’s quality of life from psychological, emotional, and social perspectives. Although hyperhidrosis is a 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. 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 mild and severe TBI. However, very little has been reported about 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. Hyperhidrosis can deteriorate a subject’s quality of life from psychological, emotional, and social perspectives. Although hyperhidrosis is a 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. 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. However, very little has been reported about PSH or hyperhidrosis in patients with mild TBI. The central regulatory center for thermoregulatory sweating is located in the hypothalamus, and hypothalamic injury has been suggested as an important pathophysiological mechanism associated with hyperhidrosis in patients with brain injuries. 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. 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. 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...
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 = 10,398 ms; echo time = 72 ms; parallel imaging reduction factor = 1000 s/mm²; number of excitations = 1; and slice thickness = 2.5 mm. Eddy current-influenced as the posterior boundary at the level of the upper midbrain 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).[33,30] 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.

### Table 1

Demographic data for the patient and control groups.

| Group   | Group A | Group B | Control group |
|---------|---------|---------|---------------|
| Sex     | 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 | – | – |
| Mean duration to DTI (months) | 13.6 (5.8) | 17.0 (6.9) | – |

Values are mean ± standard deviation.

### 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.
Several studies have reported that hyperhidrosis might be related to the concurrent presence of hyperhidrosis in the group A. Hyperhidrosis is a clinical feature of PSH, 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. 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 abnormalities in the thalamus, diencephalon, and brainstem; and (2) the excitatory: inhibitory ratio model in which paroxysms are driven by abnormalities in the thalamus, diencephalon, and brainstem.

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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**References**

[1] James WD, Berger TG, Elston DM, Odom RB. Andrews’ diseases of the skin: clinical dermatology. 10th edn. Philadelphia: Saunders Elsevier. 2006.

[2] Vary JC Jr. Selected disorders of skin appendages—acne, alopecia, hyperhidrosis. Med Clin North Am. 2015;99:1195–211.

[3] Rabinstein AA. Paroxysmal sympathetic hyperactivity in the neurologist. Ann Neurol. 2010;68:126–35.

[4] Perkes IE, Menon DK, Nott MT. Paroxysmal sympathetic hyperactivity in severe traumatic brain injury. Acta Neurochir. 2017;16:721–9.

[5] Meyfroidt G, Baguley IJ, Menon DK. Paroxysmal sympathetic hyperactivity: the storm after acute brain injury. Lancet Neurol. 2017;16:721–9.

[6] Mathew MJ, Deepika A, Shukla D, Devi BI, Ramesh VJ. Paroxysmal sympathetic hyperactivity in severe traumatic brain injury. Acta Neurochir (Wien). 2016;158:2047–52.
Jang SH, Kwon YH, Lee SJ. Tachycardia in a patient with mild traumatic brain injury. Clin Auton Res. 2019;30:87-89.

Schlereth T, Dieterich M, Birklein F. Hyperhidrosis—causes and treatment of enhanced sweating. Dtsch Arztebl Int. 2009;106:32–7.

Low PA, Benarroch EE. Clinical autonomic disorders. 3rd edn. Philadelphia: Lippincott Williams & Wilkins. 2008.

Baguley IJ, Heriseanu RE, Cameron ID, Nott MT, Sloewa-Younan S. A critical review of the pathophysiology of dysautonomia following traumatic brain injury. Neurocrit Care. 2008;8:293–300.

Pranzatelli MR, Pavlakis SG, Gould RJ, De Vivo DC. Hypothalamic-midbrain dysregulation syndrome: hypertension, hyperthermia, hyperventilation, and decerebration. J Child Neurol. 1991;6:115–22.

Thorley RR, Wertsch JJ, Klingbeil GE. Acute hypothalamic instability in traumatic brain injury: a case report. Arch Phys Med Rehabil. 2001;82:246–9.

Diamond A, Kenney C, Almaguer M, Jankovic J. Hyperhidrosis due to deep brain stimulation in a patient with essential tremor. Case report. J Neurosurg. 2007;107:1036–8.

Smith CA. Hypothalamic stroke producing recurrent hemihyperhidrosis. Neurology. 2001;56:1394–6.

Sakashita Y, Kakuta K, Kakuma K, Matsuda H. Unilateral persistent hyperhidrosis after ischemic stroke. Rinsho Shinkeigaku. 1992;32:454–6.

Ueno M, Tokunaga Y, Terachi S, Gondo K, Harai T. Asymmetric sweating in a child with multiple sclerosis. Pediatr Neurol. 2000;23:74–6.

Affi AK, Bergman RA. Functional neuroanatomy: text and atlas. 2nd edn. New York: Lange Medical Books/McGraw-Hill. 2005.

Lee SJ, Jang SH. Hypothalamic injury in spontaneous subarachnoid hemorrhage: a diffusion tensor imaging study. Clin Auton Res. 2021;31:321–2.

Jang SH, Seo YS. Neurogenic fever due to injury of the hypothalamus in a stroke patient: case report. Medicine (Baltim). 2021;100:e24053.

Jang SH, Kwon HG. Injury of the hypothalamus in patients with hypoxic-ischemic brain injury: a diffusion tensor imaging study. Am J Phys Med Rehabil. 2018;97:160–3.

Menzel K, Belke M, Unger MM, et al. DTI reveals hypothalamic and brainstem white matter lesions in patients with idiopathic narcolepsy. Sleep Med. 2012;13:736–42.

Shen Y, Bai L, Gao Y, et al. Depressive symptoms in multiple sclerosis from an in vivo study with TBSS. Biomed Res Int. 2014;2014:148463.

Jang SH, Yi JH, Kim SH, Kwon HG. Relation between injury of the hypothalamus and subjective excessive daytime sleepiness in patients with mild traumatic brain injury. J Neurol Neurosurg Psychiatry. 2016;87:1260–1.

Hanken K, Eling P, Kastrup A, Klein J, Hildebrandt H. Integrity of hypothalamic fibers and cognitive fatigue in multiple sclerosis. Mult Scler Relat Disord. 2015;4:39–46.

Alexander MP. Mild traumatic brain injury: pathophysiology, natural history, and clinical management. Neurology. 1995;45:1253–60.

Solish N, Bertucci V, Dansecreau A, et al. A comprehensive approach to the recognition, diagnosis, and severity-based treatment of focal hyperhidrosis: recommendations of the Canadian hyperhidrosis advisory committee. Dermatol Surg. 2007;33:908–23.

Duvernoy HM, Bourguin P. The human brain: surface, three-dimensional sectional anatomy with MRI, and blood supply. 2nd completely rev. and enl. edn. Wien; New York: Springer. 1999.

Jiang H, van Zijl PC, Kim J, Pearson GD, Mori S. DtiStudio: resource program for diffusion tensor computation and fiber bundle tracking. Comput Methods Programs Biomed. 2006;81:106–16.

Assaf Y, Pasternak O. Diffusion tensor imaging (DTI)-based white matter mapping in brain research: a review. J Mol Neurosci. 2008;34:51–61.

Neil JJ. Diffusion imaging concepts for clinicians. J Magn Reson Imaging. 2008;27:1–7.

Godoy DA, Panhke P, Guerrero Suarez PD, Murillo-Cabezas F. Paroxysmal sympathetic hyperactivity: an entity to keep in mind. Med Intensiva. 2019;43:35–43.

Lee SK, Kim DI, Kim J, et al. Diffusion-tensor MR imaging and fiber tractography: a new method of describing aberrant fiber connections in developmental CNS abnormalities. Radiographics. 2005;25:53–65; discussion 66-8.