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STRUCTURAL CHANGES IN THE CNS OF PATIENTS WITH HEMIFACIAL SPASM

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Abstract—Hemifacial spasm (HFS) is a peripheral nerve disorder which impacts the living quality of patients both psychologically and physically. Whether HFS has structural changes under these specific stressors including psychological and physiological conditions in the CNS remains largely unknown. In the current study, voxel-based morphometry (VBM) was used to evaluate changes in gray matter (GM) by using T1-weighted imaging in 25 HFS patients and 25 demographically similar healthy volunteers. The severity of the spasm was assessed using a Cohen evaluation scale. Hamilton anxiety (HAMA) and Hamilton depression (HAMD) rating scales were used to evaluate the affective conditions of subjects. 3D-FIESTA and 3D-TOF sequences were applied to evaluate the neurovascular compression (NVC) rating in each subject. In our results, we found that HFS patients had higher NVC rating scores than those of healthy volunteers, and the spasm severity rating was positively correlated with the NVC rating ($r = 0.736$, $p < 0.001$). HFS patients had higher scores on the HAMA and HAMD compared with healthy volunteers. For the GM comparison, reductions were found in the thalamus, putamen, pallidum, dorsolateral prefrontal cortex, amygdala and parahippocampal gyrus in patients with HFS compared with healthy volunteers. Additionally, the GM volume changes in the amygdala did not exhibit any significant between-group differences with HAMA and HAMD scores as covariates. Our results suggested that HFS probably led to GM volume abnormalities of the CNS. We indicated that the GM volume changes of the amygdala may be highly related to emotional factors.

Key words: hemifacial spasm (HFS), voxel-based morphometry (VBM), emotional factors, stressors.

INTRODUCTION

Hemifacial spasm (HFS) is a neuromuscular movement disorder generally characterized by unilateral, involuntary, and intermittent contractions of the muscles innervated by the ipsilateral facial nerve (cranial nerve VII) (Wang and Jankovic, 1998; Rosenstengel et al., 2012). It often initially involves the orbicularis oculi muscle, gradually extending to the whole hemiface (Wang and Jankovic, 1998; Au et al., 2004; Rosenstengel et al., 2012). Patients with HFS suffer from pronounced spasm of the facial muscles which frequently causes social embarrassment, have mental distress and this impacts their quality of life (Wang et al., 2014). In HFS patients, depression and anxiety are more common than in the normal population (Tan et al., 2005; Rosenstengel et al., 2012) and stress, anxiety, and depression can frequently exacerbate the symptoms and vice versa (Tan et al., 2005). Intermittent spasm of the facial muscles and accompanied emotional factors may act as stressors that may, in a vicious cycle, lead to further depression, anxiety and worsen symptoms. Stressors have been reported to activate the autonomic nervous system and neuroendocrine mechanisms in a way that may be adaptive or maladaptive, and even change the structure of the CNS (Borsook et al., 2012). Few studies have focused on the structural changes in the CNS caused by HFS.

Shimizu et al. hypothesized that there was a metabolic increase in the thalamus and cerebellum in HFS patients and measured glucose metabolism using positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose in HFS patients. They found that patients with HFS showed bilateral cerebral glucose hypermetabolism in the thalamus compared with healthy controls (Shimizu et al., 2012). Numerous studies have reported that chronic vascular contact or compression of the root exit zone of the facial nerve is widely accepted as the most probable potential etiology of HFS (Wang and Jankovic, 1998; Rosenstengel et al., 2012), thus they suggested that glucose hypermetabolism in the thalamus was considered more as a secondary change than a predisposition of HFS (Shimizu et al., 2012). Their studies provided evidence that abnormal changes existed in the CNS of HFS patients.

On the other hand, the symptoms of HFS patients always begin with involuntary contractions of the orbicularis oculi muscle, similar with essential blepharospasm, a form of focal dystonia (Jinnah et al., 2013) which has been connected with basal ganglia dysfunction (Broocks et al., 1998; Aleman et al., 2009; Dias

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Abbreviations: BoNT-A, botulinum neurotoxin type A; CNS, central nervous system; FWE, family-wise error; GM, gray matter; HAMA, Hamilton anxiety; HAMD, Hamilton depression; HFS, hemifacial spasm; MRI, magnetic resonance imaging; NVC, neurovascular compression; PET, positron emission tomography; TFCE, threshold-free cluster enhancement; VBM, voxel-based morphometry.

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et al., 2009), and is frequently confounded clinically with HFS. Aleman et al. evaluated the systematic cognitive performance of blepharospasm patients using a series of Cognitive Assessment Tests and reported that the patients were associated with cognitive disturbances (Aleman et al., 2009). Previous studies elucidated that both HFS and blepharospasm had a common condition that frequently led to emotional and social distress (Tucha et al., 2001; Setthawatcharawanich et al., 2011). Patients with blepharospasm or HFS suffer primarily from associated psychosocial stress and this often leads patients to avoid social contact (Scheidt et al., 1996; Tucha et al., 2001; Setthawatcharawanich et al., 2011). In contrast, the hormonal responses may be influenced under these specific stressors, even leading to brain network structural changes (Roozendaal et al., 2009; Borsook et al., 2012). Studies using voxel-based morphometry (VBM) showed gray matter (GM) abnormalities in the putamen (Etgen et al., 2006), thalamus (Obermann et al., 2007) and the primary sensorimotor cortex (Suzuki et al., 2011) in patients with blepharospasm. To the best of our knowledge, few studies have investigated morphological changes of HFS. Here, we hypothesized that abnormal morphological changes also could be detected in the CNS of HFS.

To test our hypothesis, we analyzed the whole-brain GM volume using VBM in 25 HFS patients and 25 demographically similar healthy volunteers in the present study.

EXPERIMENTAL PROCEDURES

Subjects

Twenty-five patients (14 women, 11 men; mean age 48.44 ± 12.27 years), who were diagnosed as having primary HFS according to medical history and typical facial muscle spasms that are unilateral, involuntary, and had intermittent contractions innervated by the ipsilateral facial nerve, were recruited from the Neurosurgery and Neurology Department of the First Affiliated Hospital of Xi'An Jiaotong University College of Medicine. Twenty-five demographically similar healthy volunteers (14 women, 11 men; mean age 49.12 ± 12.35 years) were used as the control group. All subjects were right handed. Exclusion criteria: (1) have secondary HFS caused by a tumor or surgery of the cerebellopontine angle, (2) have dementia senilis, an organic brain disorder, or severe neurological or psychiatric disorders, (3) have contraindications for an magnetic resonance imaging (MRI) scan (e.g., cardiac pacemaker implants or claustrophobia), (4) have other diseases, such as hypertension, diabetes or coronary disease, and (5) none of the subjects were using neuropsychiatric drugs and none of the HFS patients accepted treatment using botulinum neurotoxin type A (BoNT-A). For demographics and patient characteristics see Table 1.

We state that this study was approved by the ethics committee of the First Affiliated Hospital of Xi'An Jiaotong University College of Medicine and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all of the subjects before the study.

Questionnaires

By using a Cohen evaluation scale (Cohen et al., 1986) (0–4 scale: 0 = none; 1 = increased blinking caused by external stimuli; 2 = mild, noticeable fluttering, not incapacitating; 3 = moderate, very noticeable spasm, mildly incapacitating; 4 = severely incapacitating (unable to drive, read, etc.)), the severities were assessed. Besides, all of the subjects underwent the Hamilton anxiety (HAMA) and Hamilton depression (HAMD) rating scales before MR scanning to evaluate the affective conditions.

MRI data acquisition

MRI was performed on a GE HDxt 3.0 T MRI system using a three-dimensional T1-weighted fast spoiled gradient echo sequence with the following parameters: repetition time = 10.7 ms, echo time = 4.9 ms, matrix size = 256 × 256, field of view = 256 mm × 256 mm, slice thickness = 1 mm, space between slices = 0, 136 axial slices, scan duration = 4 min and 51 s. T1- and T2-weighted images were performed to exclude an organic disorder of the brain. Furthermore, 3D-FIESTA and 3D-TOF sequences were analyzed to evaluate the neurovascular compression (NVC) rating in the root exit zone of facial nerves in patients with HFS. Oblique sagittal and coronal reconstructed 3D-FIESTA images

Table 1. Summary of demographic, clinical, and MRI data of the participants

Demographic and psychometric variables	Group (range)		*P* value
	HFS patients ($\bar{x} \pm s$)	Controls ($\bar{x} \pm s$)	
Number of subjects	25 (female = 14)	25 (female = 14)	
Mean age (years ± SD)	48.44 ± 12.27	49.12 ± 12.35	0.846
Disease duration (years)	3.33 ± 3.58	–	–
HAMA scores	5.24 ± 2.88	0.24 ± 0.60	0.000*
HAMD scores	4.96 ± 2.81	0.24 ± 0.83	0.000*
Cohen scores	2.88 ± 0.78	–	–
NVC scores	1.80 ± 0.91	0.12 ± 0.33	0.000*

$\bar{x}$ = mean; s = standard deviation; HAMA = Hamilton anxiety; HAMD = Hamilton depression; Cohen scores = spasm severity rating via the Cohen evaluation scale; NVC scores = neurovascular compression rating scores.

* Significant difference between groups.