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Acupuncture-induced cerebral blood flow responses in dystonia

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Objective: The effect of acupuncture (ACP) on regional cerebral blood flow (rCBF) is unclear. Single-photon emission computed tomography studies on three patients with dystonia were performed before and after ACP treatment to test the contention that ACP affects rCBF. ***Methods:*** Pre-ACP and post-ACP CBF study were performed on the same day; ^{99m}Tc ethyl cysteinate dimer was injected for each study. rCBF images were analyzed using a three-dimensional stereotaxic ROI template (3DSRT) to objectively measure rCBF. We evaluated rCBF bilaterally in five segments related to the pathophysiology of dystonia (1, superior frontal; 2, middle and inferior frontal; 3, primary sensorimotor; 4, lenticular nucleus; and 5, thalamus). More than 10% left-right asymmetry in rCBF over three continuous slices was defined as significant laterality. Post-ACP rCBF and laterality were evaluated with the pre-ACP rCBF study acting as a control in each subject. ***Results:*** The clinical effect of ACP was remarkable in all patients and rCBF increased in most segments. Pre-ACP rCBF exhibited significant laterality in eight segments of the three patients. Laterality reversed in seven of these segments and resolved in the remaining segment after ACP. Pre-ACP rCBF laterality was not preserved in any segment after ACP. The remaining five segments exhibited laterality only after ACP. In total, after ACP, 13 of 15 segments demonstrated a change in CBF that was greater unilaterally. ***Conclusions:*** ACP results in an increase in CBF that is greater unilaterally. We think that unilateral change in CBF may be correlated with the action of ACP on the central nervous system in patients with dystonia.

Key words: dystonia, acupuncture, cerebral blood flow

INTRODUCTION

DYSTONIA is a syndrome characterized by sustained muscle contractions causing abnormal postures, slow involuntary torsion, or voluntary movement disorder.[1] The pathophysiology of dystonia remains unclear; most lesions responsible for symptomatic dystonia involve the basal ganglia and thalamus.[2] It has been assumed that biochemical changes in the basal ganglia are responsible for idiopathic dystonia and that disruption of circuits connecting the basal ganglia, thalamus, and frontal cortex gives rise to secondary dystonia.[3,4]

No consistent anatomical pathology has been found in primary dystonia. Positron emission tomography (PET) using fluorodeoxyglucose (^{18}FDG) and $H_2{}^{15}O$ has produced inconsistent results: striatal glucose utilization and resting blood flow have been reported to be raised,[5] normal,[6] and reduced,[7] and activity in the mesial frontal cortex has been reported to be raised[8] and reduced.[7]

Acupuncture (ACP) is largely used for pain control in several pathological conditions. It is hypothesized that its effects on the central nervous system might involve endogenous opioid ligands.[9,10] Several recent studies have demonstrated specific effects of ACP on cerebral blood flow using PET[11] or functional magnetic resonance imaging.[12] However, these studies were mostly conducted in normal volunteers; there has been little research of this kind in patients with CNS disorders. In this study, we measured CBF using single photon emission computed

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tomography (SPECT) before and after ACP to assess the effect of ACP on the central nervous system in dystonia.

MATERIALS AND METHODS

Subjects:
Three patients with dystonia (one woman and two men; age range 32–52 years) were examined after obtaining their informed consent. Etiology and clinical symptoms are summarized in Table 1.

Data Acquisition:
Evaluation of CBF was performed according to the one-day protocol of Takeuchi et al.[13] Briefly, prior to ACP treatment, preliminary (control) CBF scintigraphy was performed for each subject with 400 MBq of technetium-99m ethyl cysteinate dimer (Daiichi Radioisotope Laboratories, Tokyo, Japan; ^{99m}Tc-ECD) provided in a kit. Dynamic data were collected for 120 seconds at one frame/second using a large-field-of-view gamma camera (E.CAM, Toshiba Co., Tokyo, Japan). Subjects lay in the supine position in a quiet room, facing the detector and wearing eye masks. After collection of the dynamic data, cerebral SPECT scanning was performed using a three-head SPECT system (GCA 9300A/DI, Toshiba Co., Tokyo, Japan) equipped with high-resolution fan-beam collimators. Projection data were obtained using a matrix size of 128 × 128 with a total of 4 rotations, at one-rotation/5 minutes. Acquired SPECT images were reconstructed by filtered back-projection using a Butterworth filter and a ramp filter. Attenuation correction was carried out using Chang's method with $\mu = 0.15$. The triple-

Table 1 Clinical summary and data of acupuncture of patients with dystonia

Patient no.	Age	Sex	etiology	clinical presentation	Acupuncture site/time	Purpose of acupuncture	Effects of acupuncture
1	52	M	idiopathic	rotatocollis	LI4 (Hegu)		
					: Rt/20 min	facilitation of right SCM	
					: Lt/10 min	inhibition of left SCM	Normalized position
2	37	M	drug-induced	opisthotonus of trunk and neck	ST42 (Chongyang) : Bil/20 min	facilitation of bilateral truncal muscles	Normalized position
3	32	F	drug-induced	lateral bending of trunk	ST42 (Chongyang) : Lt/10 min	facilitation of left flank muscles	Normalized position

Rt; right, Lt; left, Bil; bilateral, SCM; sternocleidomastoid muscle

Table 2 CBF data, left-right asymmetry, and increased rate of CBF before and after acupuncture

Patients no./Segments	Pre-ACP CBF/asymmetry			Post-ACP CBF/asymmetry			Increase in CBF after ACP (%)	
	R	L		R	L		R	L
Patient 1								
Superior frontal	28.2	25.0	R > L	28.8	36.4	L > R	2	46
Middle and inferior frontal	43.2	38.6	R > L	44.7	55.3	L > R	4	43
Primary sensorimotor	36.6	38.6		47.4	40.3	R > L	30	4
Lenticular nucleus	47.5	39.8	R > L	50.6	56.3	L > R	6	41
Thalamus	44.2	55.3	L > R	59.8	53.5	R > L	35	–3
Patient 2								
Superior frontal	43.1	43.4		51.7	59.5	L > R	20	37
Middle and inferior frontal	44.1	46.5		61.0	54.0	R > L	38	16
Primary sensorimotor	46.8	56.9	L > R	65.5	57.2	R > L	40	0
Lenticular nucleus	52.5	62.6	L > R	86.7	84.4		65	35
Thalamus	60.2	54.2	R > L	67.9	75.7	L > R	13	40
Patient 3								
Superior frontal	44.0	43.3		48.6	48.1		10	11
Middle and inferior frontal	48.9	43.9	R > L	48.6	55.2	L > R	0	26
Primary sensorimotor	44.3	43.5		41.8	53.1	L > R	–5	22
Lenticular nucleus	54.8	53.5		52.0	54.0		–5	1
Thalamus	57.2	60.1		81.3	68.0	R > L	42	13

ACP; acupuncture

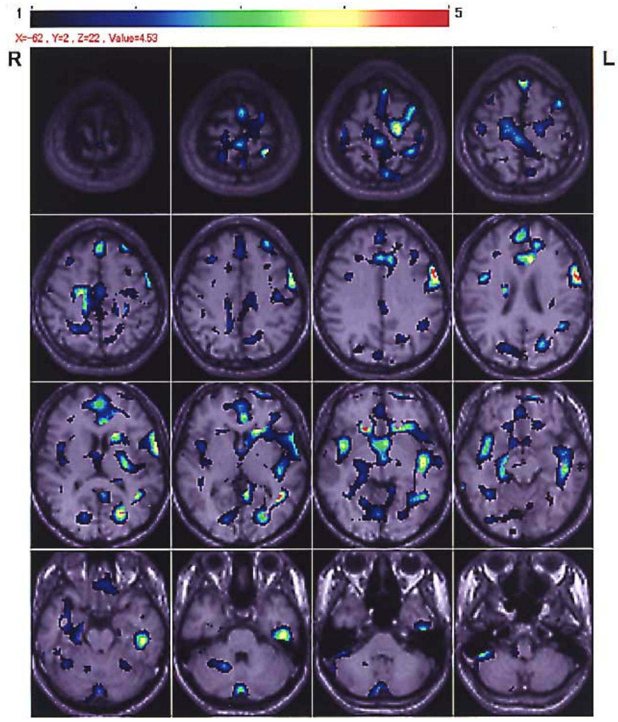

Fig. 1 Statistical parametric map of the *t* statistic in a 52-year-old man (patient 1) obtained SPECT data before acupuncture. The eZIS shows significantly decreased cerebral regions of rCBF compared with a shared normal database.

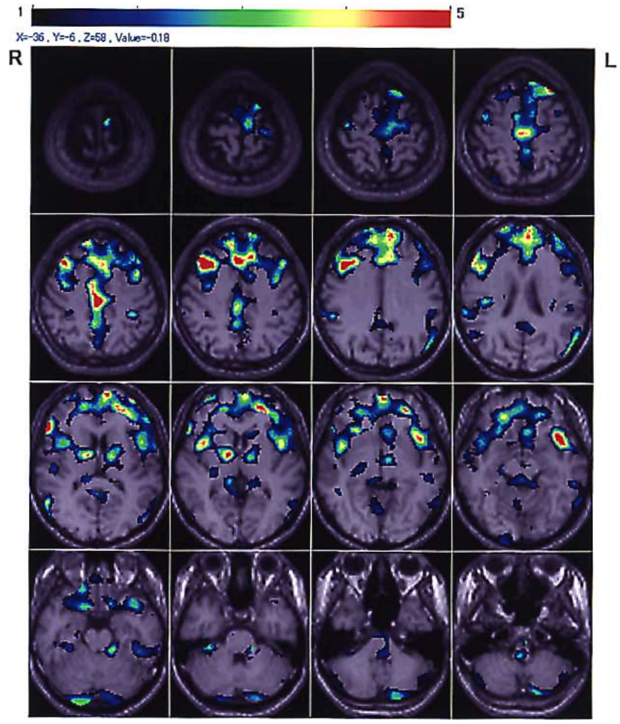

Fig. 2 Statistical parametric map of the *t* statistic in a 37-year-old man (patient 2) obtained SPECT data before acupuncture. The eZIS shows significantly decreased cerebral regions of rCBF compared with a shared normal database.

energy window technique was employed for scatter correction.

After the first SPECT data acquisition, ACP treatment (described in the Results section) was performed on the examining table without any change in the patient's head position. Approximately 30 minutes after ACP, an additional 400 MBq of ^{99m}Tc-ECD was administered, and the second SPECT data acquisition was performed with conditions identical to those of the first scan. ACP-mediated change in CBF was evaluated by subtraction of the first image from the second image. After these data acquisitions, subjects left the examining table and were examined to assess the effect of ACP treatment.

Image Analysis:

To investigate relative disorders of CBF in our patients, we performed statistical analysis for the first CBF image using the easy Z-score imaging system (eZIS),[14] which provides a z-score for SPECT images by comparison to a shared normal database using Statistical Parametric Mapping 99 software. Hoffmann 3-dimensional brain phantom data were used to correct the difference of collimators and reconstruction processes between ours and normal database.

To investigate absolute values and changes of CBF between baseline and after ACP, regions-of-interest (ROIs) in a total of 59 slices were drawn with automated ROI

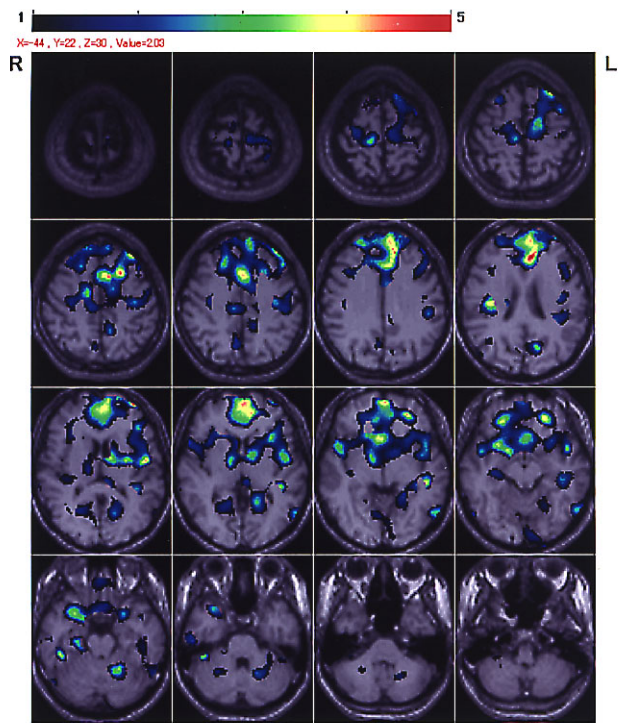

Fig. 3 Statistical parametric map of the *t* statistic in 32-year-old woman (patient 3) obtained SPECT data before acupuncture. The eZIS shows significantly decreased cerebral regions of rCBF compared with a shared normal database.

analysis software for the brain (a three-dimensional stereotaxic ROI template, 3DSRT).[15]

To evaluate laterality of cerebral blood flow, asymmetric index (AI) was calculated as follows:

$$\text{AI}\ (\%) = \frac{(\text{CBFright} - \text{CBFleft})}{(\text{CBFright} + \text{CBFleft})} \times 2 \times 100.$$

Macro sheets were used to calculate AI and changes in cerebral blood flow after ACP.

Of the 12 segments obtained from 3DSRT, we evaluated five segments on each side in the present study: (1, superior frontal; 2, middle and inferior frontal; 3, primary sensorimotor; 4, lenticular nucleus; and 5, thalamus), which are considered to be closely involved in the pathophysiology of dystonia.[2–4] Significant left-right asymmetry was arbitrarily defined as AI > 10% over three contiguous slices in each segment. Change in CBF after ACP was only evaluated for segments that exhibited significant CBF laterality in either the first or second CBF image. If both CBF images displayed significant laterality, slices in the second CBF image were given priority over those in the first CBF image.

RESULTS

Clinical summaries and effects of ACP in the three patients are shown in Table 1. Table 2 shows CBF laterality before and after ACP and percentage increase in CBF after ACP.

Patient 1

Patient 1 had idiopathic dystonia with torticollis due to left-sided hypertonia and right-sided hypotonia of sternocleidomastoid. ACP was performed for 10 minutes at the acupoint LI4 (Hegu) on the left hand to suppress the left sternocleidomastoid and for 20 minutes at the right LI4 to stimulate the right sternocleidomastoid. Symptoms were completely relieved after ACP treatment. Figure 1 demonstrates the eZIS map of CBF before ACP. Regions of significantly impaired blood flow are demonstrated in the bilateral medial frontal gyri, left precentral gyrus, and left lenticular nucleus. There was no significantly increased area in the affected segments in dystonia. Significant left-right asymmetry before ACP was evident in four segments: three exhibited decreased left-sided blood flow and one showed diminished right-sided blood flow.

After ACP, blood flow in all segments except for the left thalamus increased bilaterally. Furthermore, increases in CBF that were greater unilaterally resulted in reversed laterality after ACP by raising CBF to a greater degree on the side that had previously exhibited impaired perfusion.

Patient 2

Patient 2 exhibited retroflexion of the neck and opisthotonus in the sitting position due to hypotonic abdominal muscles, termed “negative dystonia.” ACP was performed for 20 minutes bilaterally at the acupoint ST42 (Chongyang) on the leg to stimulate the abdominal muscles. After ACP treatment, abdominal muscle tonus was normal and the patient was able to stand unaided. Figure 2 demonstrates the eZIS map of CBF before ACP. Regions of significantly impaired blood flow were evident in the bilateral frontal lobes and bilateral lenticular nuclei. There was no significantly increased area in the affected segments in dystonia. Before ACP, significant left-right asymmetry was apparent in the primary sensorimotor and lenticular nucleus (decreased right-sided blood flow) and in the thalamus (diminished left-sided blood flow).

After ACP, in all segments other than the left primary sensorimotor segment, blood flow increased bilaterally; furthermore, CBF increased to a greater degree unilaterally, resulting in left-right asymmetry in four segments. Among these four segments, laterality reversed after ACP in two segments and the other two segments exhibited laterality only after ACP. In the remaining segment, laterality resolved after ACP; this was also due to a predominant increase in blood flow in the side that had previously shown diminished perfusion.

Patient 3

Patient 3 exhibited flexion of the trunk to the left in the sitting position due to a hypotonic left flank muscle; i.e. a similar mechanism to that observed in patient 2. ACP was performed for 10 minutes at the acupoint ST42 on the left leg to stimulate the left-sided abdominal muscles. After ACP treatment, the impaired muscle exhibited normal tonus and a neutral sitting position could be achieved. Figure 3 demonstrates the eZIS map of CBF before ACP. Regions of significantly impaired perfusion were evident in the bilateral frontal lobes, including the superior, middle, inferior, and medial frontal gyrus, left precentral gyrus, and bilateral lenticular nuclei. There was no significantly increased area in the affected segments in dystonia. Before ACP, significant left-right asymmetry was evident in the middle and inferior frontal gyrus (left-sided impaired perfusion). After ACP, CBF increased to a greater extent on the side that had previously shown low perfusion, producing reversed laterality in the left middle and inferior frontal gyrus and inducing CBF laterality in the other two regions.

Summary of Results:

In summarizing the results of left-right CBF asymmetry in a total of 15 segments in the three patients; significant asymmetry on the first CBF reversed after ACP in seven segments (47%) and resolved in one (7%), while significant asymmetry appeared only after ACP in five (33%). Therefore, 13 segments (87%) demonstrated an increase in CBF that was greater unilaterally. Asymmetrical patterns of blood flow seen on preliminary CBF were not maintained in any segments after ACP.

DISCUSSION

This preliminary study demonstrated several effects of ACP on CBF in dystonic patients. ACP increased CBF in almost all segments, and most segments (13/15, 87%) showed significant unilateral changes in CBF. Significant laterality was not maintained in any segments preserved after ACP.

Most previous reports on the effect of ACP on the central nervous system (CNS) using PET[11] or fMRI[12] have been confined to healthy volunteers. The literature contains few reports of such effects of ACP in patients with CNS disease and to the best of our knowledge, the present study is the first to examine the effects of ACP on CBF in dystonic patients.

While the exact mechanisms behind the present findings have yet to be elucidated, the following two hypotheses can be raised. First, unilateral impairment of CBF might be associated with the pathophysiology of dystonia. Second, the therapeutic action of ACP in dystonia might be related to a unilateral increase in CBF on the impaired side, resulting in favorable clinical results.

It is possible to speculate that the unilateral increase in CBF is closely correlated to the action of ACP. This would suggest that the therapeutic mechanism of ACP involved correcting pathological muscle tonus that was observed in patients with dystonia. The pathophysiology of dystonia involves the basal ganglia, thalamus, and frontal cortex.[2–4] This is consistent with the findings of this study, which showed statistically significant diminished rCBF (Z score > 2) on eZIS. Previously published papers have presented conflicting results regarding rCBF/CMRGlc in patients with dystonia. However, areas associated with dystonia in the central nervous system are consistently frontal cortex, basal ganglia, and thalamus. In our subjects no increase in these areas was depicted by the eZIS. Furthermore, our subjects all demonstrated symptomatic improvements and most rCBF increased after effective ACP. It is therefore possible that the finding of low CBF in these areas is related to the pathophysiology of dystonia.

In these areas, 3DSRT revealed significant left-right CBF asymmetry (more than 10% in over three slices) before ACP, which reversed after ACP due to a larger increase of perfusion in the side with previously diminished CBF. This finding also supports a relationship between CBF and the pathophysiologic mechanism of dystonia. The finding of increased CBF that was greater unilaterally as a result of ACP represents novel and important evidence that ACP affects the central nervous system.

Unfortunately, because of the small number of patients and inconsistent etiology, symptom location, and muscle tonus in this study, it was not possible to explain systematically how CBF increase is related to symptomatic improvements.

In summary, we believe that unilaterally dominant changes in CBF correlated well with the action of ACP on the central nervous system in patients with dystonia.

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