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ORIGINAL COMMUNICATION

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Glucose hypermetabolism in the thalamus of patients with essential blepharospasm

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Abstract Essential blepharospasm (EB) is classified as a form of focal dystonia characterized by involuntary spasms of the musculature of the upper face. The basic neurological process causing EB is not known. The purpose of this study was to investigate cerebral glucose metabolism in patients with EB whose symptoms were suppressed by an injection of botulinum-A toxin. Earlier studies were confounded by sensory feedback activities derived from dystonic symptom itself. Cerebral glucose metabolism was examined by positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) in 25 patients (8 men and 17 women; age 52.6 ± 10.1 years) with EB. The patients were awake but with the spasms suppressed by an injection of botulinum-A toxin. Thirty-eight normal volunteers (14 men and 24 women; age 58.2 ± 7.3 years) were examined as controls. The difference between the two groups was examined by statistical parametric mapping (SPM99). A significant increase in the glucose metabolism was detected in the thalamus and pons in the EB patients. Hyperactivity in the thalamus may be a key pathophysiological change common to EB and other types of focal dystonia. The activity of the striatum and cerebellum are likely to be sensory dependent.

Key words essential blepharospasm · focal dystonia · glucose metabolism · positron emission tomography · thalamus

Introduction

Essential blepharospasm (EB) is a form of focal dystonia characterized by involuntary spasms of the musculature of the upper face. Earlier studies have reported a glucose hypermetabolism in the thalamus and basal ganglia in patients with dystonia, and it has been widely held that dysfunction of cortical-striato-thalamo-cortical motor circuits may have a major role in the pathophysiology of dystonia [1]. It has also been reported that dystonia is caused by thalamic infarctions [2], and patients with EB have been reported to be associated with increased glucose metabolism in the thalamus [3] and cerebellum [4] by positron emission tomography (PET) studies using ^{18}F-fluorodeoxyglucose (FDG).

There have been several studies on other forms of focal dystonia using PET. In patients with spasmodic torticollis, Galardi et al. reported hypermetabolism in the thalamus, basal ganglia, anterior cingulate gyrus,

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and cerebellum [5], and Eidelberg et al. found a relative increase of metabolic activity in the lentiform nucleus and premotor cortices of patients with idiopathic torsion dystonia [6]. In EB and other dystonias, the majority of the studies have demonstrated a hypermetabolism of the thalamus and basal ganglia. A common limitation of earlier neuroimaging studies of dystonia lies in that they observed integral brain activities reflecting both the cause and the consequence of abnormal involuntary movements.

In order to separate the effects of cause and consequence on EB, Hutchinson et al. measured the glucose metabolism of EB patients during wakefulness and during induced sleep because the involuntary movements disappear during sleep. They found a hypermetabolism in the cerebellum and pons only during wakefulness [4]. However they could not find the primary cause of EB during sleep.

We hypothesized that the hyperactivity in the thalamus and basal ganglia is not a secondary phenomenon accompanies the abnormal movement, but is a primary pathophysiological condition that cause the symptoms. To test this hypothesis and to determine the responsible cerebral regions, PET measurements were made to evaluate regional cerebral glucose metabolism while the patients were awake, but the involuntary eyelid movements were suppressed by a botulinum toxin-A injection.

Materials and methods

Twenty-five patients (8 men and 17 women; age 52.6 ± 10.1 years), who visited the Ophthalmology Outpatient Clinic of Tokyo Medical and Dental University Hospital and were diagnosed with bilateral EB, were studied. The mean duration of their illness was 2.9 ± 3.3 years. None had an organic brain disorder or other neuro-psychiatric disease as evaluated by neurologists from conventional diagnostic magnetic resonance images (MRIs). No one had a family history of dystonic disorders. Patients who had not taken any neuro-psychiatric drugs such as neuroleptic drugs, antidepressant drugs, anti-Parkisonian drugs, and anti-epileptic drugs were selected by careful history taking to exclude drug-related cases because drug related cases might confound [7]. Thirty-eight normal volunteers (14 men and 24 women; age 58.2 ± 7.3 years) were recruited as the normal control group. Normal subjects had no organic brain disorders or neuro-psychiatric disease, and had not taken any neuro-psychiatric drugs.

Informed consents were obtained from all the subjects before participation in the PET study. This study protocol was approved by the Institutional Ethics Committee. All of the procedures conformed to the tenets of the Declaration of Helsinki.

All of the patients received an injection of botulinum-A toxin (18 to 36 units bilaterally) into the orbicularis oculi (OO) muscle, and the PET scans were obtained when the spasms of the OO were effectively restrained. PET scanning was done in the time when the spasm of eyelids was depressed after the botulinum toxin treatments within three months. The severity of blepharospasm was assessed with the 0 to 4 (0 = absent, 4 = most severe), and the frequency of blepharospasm was assessed with the 0 to 4 (0 = none, 4 = persistent eye closure), too in accordance with the classification of Jankovic [8]. We evaluated the severity and frequency of the spasm in all the patients before the latest treatment of botulinum toxin and at the time of the PET study, actually between the injection of FDG and the scanning (Table 1). As not all the patients have reached complete suppression of blepharospasm at the moment of PET scan by botulinum-A toxin treatment, we divided the patients into two subgroups for further analysis, based on the on-site evaluation of the blepharospasm symptom: complete suppression group (n = 12; 5 men and 7 women; age 56.2 ± 9.5 years, severity 0, frequency 0) and incomplete suppression group (n = 13, 3 men and 10 women; age 48.8 ± 8.4 years, severity 1 ± 1, frequency 1 ± 1). There was no significant difference in symptomatic scores before treatment between incomplete suppression group (3.00, 3.00), and complete suppression group (3.08, 2.83). The only significant difference ($p < 0.05$) was the duration of illness: 1.50 ± 1.2 years in complete suppression group and 4.15 ± 4.1 years in incomplete suppression group.

MRI scans were obtained from all of the subjects to screen for organic brain disorders with a 1.5 Tesla scanner Signa Horizon (General Electric, Milwaukee). Transaxial images with T1-weighted contrast (3DSPGR, TR = 9.2 ms, TE = 2.0 ms, matrix size = 256 × 256 × 124, voxel size = 0.94 × 0.94 × 1.3 mm), and T2-weighted contrast (First Spin Echo, TR = 3,000 ms, TE = 100 ms, matrix size = 256 × 256 × 20, voxel size = 0.7 × 0.7 × 6.5 mm) were obtained. None of the subjects showed any abnormalities in brain morphology and intensities.

PET data acquisition

PET scans were obtained with the Headtome-V scanner SET 2400W (Shimadzu, Kyoto, Japan) at the Positron Medical Center, Tokyo Metropolitan Institute of Gerontology. Attenuation was corrected by a transmission scan with a $^{68}Ga/^{68}Ge$ rotating source. For the PET scan, a bolus of 120 MBq FDG was injected intravenously. Each patient was then requested to lie down comfortably with their eyes closed. A 6-minute emission scan in 3D acquisition mode was started 45 minutes after the injection, and 50 transaxial images with an interslice interval of 3.125 mm were obtained. The tomographic images were reconstructed using a filtered backprojection method, and Butterworth filter (cutoff frequency 1.25 cycle/cm and order of 2).

Data processing and statistical analysis

PET images were processed and analyzed with the statistical parametric mapping (SPM99) software [9] implemented in Matlab (Mathworks., Sherborn, MA, USA). Statistical parametric maps combine the general linear model and the theoretical Gaussian fields to make statistical inferences about regional effects. All PET images were spatially normalized to a standard template produced by Montreal Neurological Institute using the housemade template of FDG-PET images and smoothed with Gaussian filter for 16 mm FWHM to increase the signal to noise ratio before statistical processing.

After the appropriate design matrix was specified, the subject and group effects were estimated according to the general linear model at each voxel. We selected (compare-populations: 1 scan/subjects (two sample t-test)) in design type, and selected (global normalsation proportional scaling) in global normalization [10]. Statistical inference on the SPM (Z) was corrected using the theory of Gaussian Fields. To test hypotheses about regionally specific group effects, the estimates were compared using linear contrast. The threshold for SPM (Z) was set at $p < 0.05$ with a correction ($p < 0.05$, corrected) for the comparison between whole patient group and normal control group. We compared each of incomplete suppression group and complete suppression group to the normal control group in order to examine the effect of residual spasm. We also directly compared two subgroups each other. The threshold for SPM (Z) for the subgroup comparison was set at ($p < 0.0001$, uncorrected).

Table 1 Strength of the spasm of eyelids in EB patients

Age	Sex	Duration	Term from treatment to PET scanning	Strength of the spasm of eyelids			
				Before botulinum toxin treatment (severity, frequency)		At the time of PET scanning	
62	F	4 years	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
72	F	1 year	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
69	M	2 years	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
45	M	1 year	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
36	F	1 year	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
50	F	1 year	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
60	F	10 years	1 month	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
58	F	10 years	1 month	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
58	F	5 years	2 months	R (3, 3)	L (3, 3)	R (0, 0)	L (0, 0)
57	F	1 year	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
50	F	2 years	3 months	R (4, 3)	L (4, 3)	R (0, 0)	L (0, 0)
46	M	1 year	3 months	R (4, 3)	L (4, 3)	R (0, 0)	L (0, 0)
40	M	1 year	3 months	R (3, 3)	L (3, 3)	R (0, 0)	L (0, 0)
58	F	2 years	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
59	F	10 years	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
54	F	1 year	3 months	R (4, 3)	L (4, 3)	R (0, 0)	L (0, 0)
53	M	1 year	1 month	R (3, 3)	L (3, 3)	R (0, 0)	L (0, 0)
45	F	1 year	1 month	R (3, 3)	L (3, 3)	R (0, 0)	L (0, 0)
56	F	1 year	3 months	R (2, 2)	L (2, 2)	R (0, 0)	L (0, 0)
57	F	1 year	3 months	R (3, 3)	L (3, 3)	R (0, 0)	L (0, 0)
50	F	10 years	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
38	M	2 years	3 months	R (3, 3)	L (3, 3)	R (0, 0)	L (0, 0)
33	F	10 months	3 months	R (2, 2)	L (2, 2)	R (0, 0)	L (0, 0)
55	M	1 year	3 months	R (3, 3)	L (3, 3)	R (1, 1)	L (1, 1)
56	M	1 year	3 months	R (3, 3)	L (3, 3)	R (0, 0)	L (0, 0)
Average							
Incomp group	4.2 ± 4.1 years			R (3.00, 3.00)	L (3.00, 3.00)		
Comp group	1.5 ± 1.2 years			R (3.08, 2.83)	L (3.08, 2.83)		
Total	2.9 ± 3.3 years			R (3.04, 2.92) L (3.04, 2.92)	R (0.52, 0.52) L (0.52, 0.52)		

Severity of spasm was rated on 0 (=none) to 4 (=severe) scale[8]
Frequency of spasm was rated on 0 (=none) to 4 (=functionally blind) scale[8]
Incomp Group: incomplete suppression group
Comp Group: complete suppression group

Results

A regional glucose hypermetabolism was found in the thalamus and pons bilaterally in patients with EB ($p < 0.05$, corrected), whose eyelid spasms were decreased by botulinum-A toxin (Table 2, Fig. 1). We made mean PET images of all patients and all normal subjects. Regions of interest (ROIs), 1 cm diameter circles, were placed the thalamus and pons, respectively, due to measure the glucose metabolism levels of these regions. The mean increases were 6.5% in the thalamus and 5.3% in the pons. A trend of glucose hypermetabolism was also found in the putamen bilaterally in EB patients, but the increase was not significant ($p < 0.01$, uncorrected). There was no regional glucose hypometabolism above the statistical significant level. We found that significant hypermetabolism in the thalamus, pons and cerebellum bilaterally in incomplete suppression group

Table 2 Areas and coordinates for the maxima of regional glucose hypermetabolism in essential blepharospasm patients

Area	x	y	z	Z score
Thalamus (R)	12	−20	−2	5.00
Thalamus (L)	−8	−22	−2	5.54
Pons (R)	6	−40	−34	4.47
Pons (L)	−12	−40	−34	4.83

Areas with $Z \geq 4.17$ ($p < 0.05$, corrected) were listed

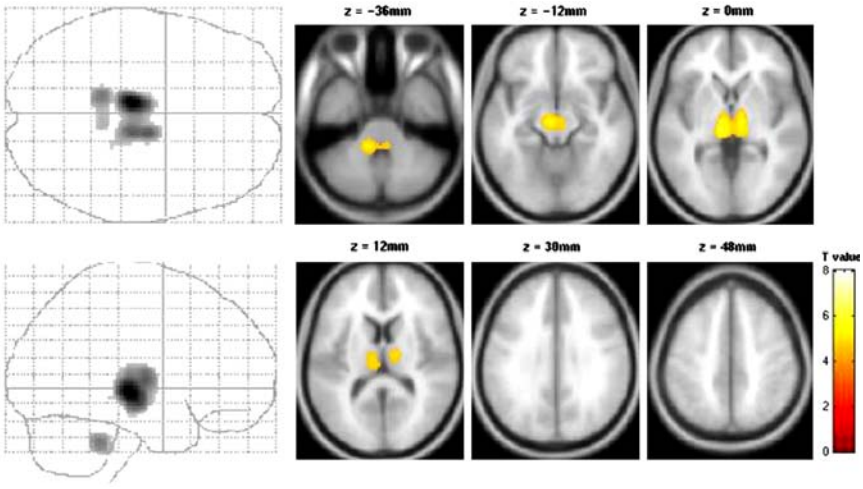

Fig. 1 Areas of glucose hypermetabolism in patients with essential blepharospasm are showed ($p < 0.05$, corrected). Left; Sagittal and transverse views of a statistical parametric map (SPM) rendered into standard stereotactic space and projected onto a glass brain. Right; Six axial slices of brain are shown. The left side of the figure corresponds to the left hemisphere

($p < 0.0001$, uncorrected) (Table 3A, Fig. 2). On the other hand, hypermetabolism was observed only in the bilateral thalamus in complete suppression group ($p < 0.0001$, uncorrected) (Table 3B, Fig. 2). However, we could not find any significant difference between incomplete suppression group and complete suppression group by direct comparison ($p < 0.001$, uncorrected).

Discussion

Effect of involuntary movements

A majority of the studies on EB and other dystonias have demonstrated hypermetabolism of the thalamus and basal ganglia, however, there is a problem in interpreting these results because these studies were performed while the patients had active symptoms of dystonia, e.g., involuntary eyelid movements in EB patients. Thus, the observed abnormal cerebral activities could be due not only to the primary cause of the dystonia, but also to the sensory input secondary from the involuntary movements. To overcome this criticism in EB patients, it is necessary to suppress the spasms of the eyelids. Hutchinson et al. hypothesized that there is metabolic increase in the thalamus and basal ganglia in EB patients because of an overactivity of a cortico-striato-thalamo-cortical motor circuit, and measured the glucose metabolism of 6 EB patients by PET while they were awake with active symptoms and while they were asleep without symptoms [4]. They found hypermetabolism in the cerebellum and pons during wakefulness, but not in the thalamus and basal ganglia during either condition. We suggest two possible reasons why they miss the hyperactivity in the thalamus and basal ganglia. First, the number of the patients and normal subjects in their study might not be enough. The difference of mean between two groups was relatively small compared to the standard deviation (difference of mean = 3.5, SD = 4.8 in the thalamus, for example), we have to increase the number of subject more than 20 to get a consistent statistical significance. Second,

Table 3 Areas and coordinates for the maxima of regional glucose hypermetabolism in incomplete suppression EB patients

Area	x	y	z	Z score
A				
Thalamus (R)	12	−10	2	3.52
Thalamus (L)	−6	−22	2	3.70
Pons (R)	2	−40	−32	5.06
Pons (L)	−6	−44	−32	5.16
Cerebellum (R)	40	−38	−38	3.58
Cerebellum (L)	−50	−48	−46	3.84
B				
Thalamus (R)	14	−20	−2	3.93
Thalamus (L)	−10	−20	−2	4.20

Areas with $Z \geq 3.45$ ($p < 0.0001$, uncorrected) were listed

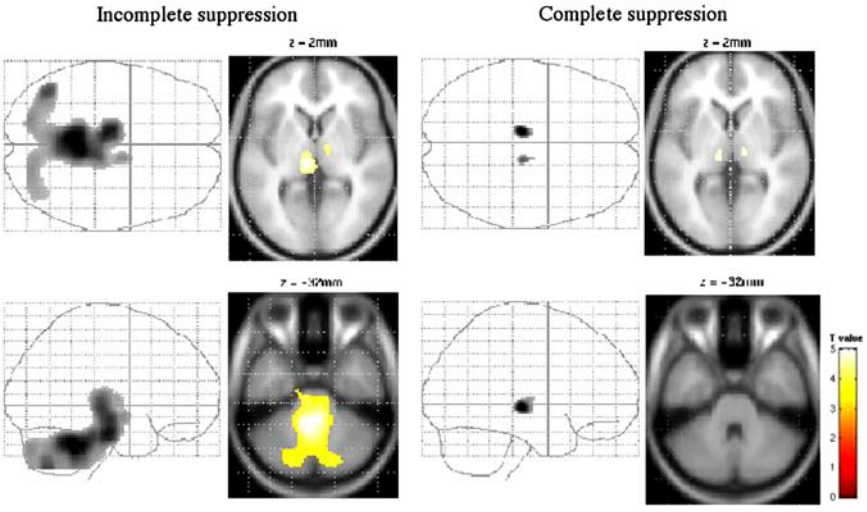

Fig. 2 Areas of glucose hypermetabolism in EB patients with incomplete suppression (left) and complete suppression (right) by botulinum toxin treatment are showed ($p < 0.0001$, uncorrected)

sleep might have depressed not only the involuntary movements but also the primary functional alteration in the brain of EB.

Ceballos-Baumann et al. examined patients with writer's cramp by PET during writing words before and after botulinum toxin treatment [11]. They found higher cerebral blood flow of patients before and after botulinum-toxin in the thalamus, left insula, bilateral premotor cortex, and bilateral primary sensory cortex than in normal subjects. In patients, activation in the cerebeller vermis was found before botulinum-toxin, but the activation disappeared after the treatment. We suggest that they succeeded in reducing the effect of involuntary movement, although the voluntary movements may still be a confounding factor.

Because the botulinum-toxin inhibits neuro-muscular conduction by a presynaptic blockade, we expected that the botulinum-toxin has minimum influence on the central causative mechanism of EB. Several previous studies have reported no significant alterations in the level of cerebral blood flow after botulinum toxin treatment [11, 12]. Therefore, in the present study, we performed a PET study in a larger size of the patients while awake and their spasms were effectively suppressed by the injection of botulinum toxin into the OO muscle bilaterally: 25 EB subjects and 38 normal controls. Under these conditions, we found a significant glucose hypermetabolism in the thalamus bilaterally in EB patients ($P < 0.05$, corrected).

Incomplete suppression group and complete suppression group

We divided EB patients to incomplete suppression group (13 patients) and complete suppression group (12 patients) based on the scores of blepharospasm at the PET scanning. There was no significant difference in severity and frequency of spasm before treatment between these 2 groups. However, the mean duration of illness of incomplete suppression group was significantly longer than that of complete suppression group. Incomplete suppression group contained 4 patients whose duration of illness was over 10 years. These patients have repeatedly been treated by botulinum toxin for a long periods. The efficacy of the treatment might have been weakened due to tolerance [13].

Regional glucose metabolism in patients with EB

Hypermetabolism in the thalamus, basal ganglia, anterior cingulate gyrus and cerebellum of patients with spasmodic torticollis using PET were reported [5]. The results of functional imaging studies are often interpreted using the present anatomical model of information flow in cortico-striato-thalamo-cortical motor circuit (Fig. 3) [14]. Based on this model, there are three possible points which might alter thalamic activity. All of them are the alterations in inhibitory synaptic functions mediated by GABAergic system. Recent reports suggest that altered GABAergic inhibition may play a role in the symptomatology of dystonia. Previous studies found a reduction of GABA levels in the sensorimotor cortex and striatum of patients with focal dystonia [16]. We suspect that a reduction of GABA levels in the striatum or thalamus might cause the hyperactivity in these areas.

Macia et al. reported that injection of bicuculline, an antagonist to $GABA_A$, into the monkey thalamus induced dystonic symptoms contralaterally and found an overactivity of thalamic neurons ipsilateral to the treatment [17]. On the other hand, Kaji reported that one of the important functions of basal ganglia is the

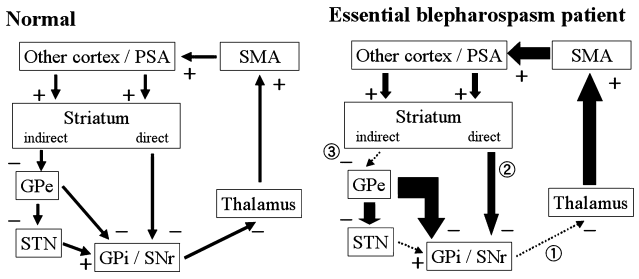

Fig. 3 Principal pathways of the normal corticobasal ganglia-cortical loops and hypothetical alterations. In the normal loops (left), the striatum receives input from the primary somatosensory area (PSA) and from other areas of the motor and sensory cortex. The striatum projects by direct and indirect pathways to the major output structures of the basal ganglia, the globus pallidus interna (GPi) and substantia nigra reticulate (SNr). An indirect pathway includes a striatal-globus pallidus externa (GPe) projection. Some GPe fibers project to the subthalamic nucleus (STN) and GPi/SNr, and other fibers project directly to the GPi/SNr. GPi/SNr, which in turn, projects to the thalamus with a subsequent feedback to motor cortex, primarily the SMA. The effect of each structure on subsequent structures is to increase (+) or decrease (−) neuronal activity as indicated, adapted from Tempel et al. [14] and Garfen [15]. For glucose hypermetabolism in the thalamus and striatum of EB patients (right), the possible points of impairments with the circuit are; 1) to impaired inhibition from GPi/SNr, 2) decreased GPi/SNr activity may result in increased activity of the direct pathway from Striatum to GPi/SNr, and 3) impaired the indirect pathway at the level of Striatum-GPe connection

gating of sensory input for motor control [18], and its alteration might cause dystonia. Previous reports found glucose hypermetabolism in EB and other focal dystonias in the striatum as well as in the thalamus [3, 5]. Recently, Schmidt et al. reported that a subregion of the putamen was active during EB spasms in patients but not during voluntary blinks in normal subjects using fMRI [19]. Perlmutter et al. have demonstrated that individuals with EB and hand dystonia have a reduced level of dopamine D_2-like receptors in the putamen relative to control subjects [20], suggesting that dopamine D_2-receptor loss disrupts lateral inhibition created by the indirect pathway of the basal ganglia. These evidences have suggested that the altered function of the putamen may be a critical component of EB. We found a trend of glucose hypermetabolism in the putamen bilaterally in EB patients, but the increase was not significant ($p < 0.01$, uncorrected). It is plausible that the hyperactivity of the striatum is sensory-input dependent. On the other hand, the hyperactivity in the thalamus was more consistent even with the depletion of sensory feedback. From these observations, hyperactivation of the thalamus may be one of the primary causes of EB, however, it might reflect a compensatory mechanism. Further investigation is required to clarify the different role of the thalamus and the striatum in the pathophysiological mechanism of EB.

We found significant hypermetabolism in the cerebellum and pons in incomplete suppression group ($p < 0.0001$, uncorrected), and not in complete suppression group ($p < 0.0001$, uncorrected) when the images of these groups were contrasted to the control group. We did not find significant difference by direct comparison of subgroups, presumably because the number of the patients in these subgroups might not be enough to reach statistical significance. The cerebellum receives extensive somatosensory input via spinocerebellar pathways, and the cerebellum would be a sensory organ [21]. Hutchinson et al. reported that EB patients exhibit hypermetabolism of the cerebellum and pons during wakefulness, but not during sleeping using PET [4]. And, Ceballos-Baumann et al. reported that patients with writer's cramp activation in the cerebeller vermis was found before botulinum-toxin, but the activation disappeared after the treatment [11]. Our results indicate that activation of the cerebellum in EB patients could be due to increased sensory input derived from involuntary muscle contraction of eyelids. Aramideh et al. reported a secondary blepharospasm patient with a small dorsomedial pontine lesion [22], and LeDoux et al. reported a secondary cervical dystonia patients due to infarctions or hemorrhage in the pons [23]. They hypothesized that abnormalities of olivocerebellar circuit and cortico-striato-thalamo-cortical motor circuit might produce similar movement disorders, and they suggested that lesions in the pons obstructed the cerebellar afferent pathways, and produced cervical dystonia.

We found significant hypermetabolism of the tegmentum in the inferior pons, and this area corresponds to the facial nucleus and facial nerve. The facial nerve is the final output pathway of focal facial dystonia from the nervous system. As the effect of botulinum-A toxin is peripheral, the facial nuclei and related structure in pons may remain hyperactive even after the treatment as we observe in our results. From these things, we suspected that hypermetabolism in the cerebellum and pons was the secondary phenomenon related to muscular activity of eyelids.

Conclusions

A glucose hypermetabolism was detected in the thalamus and pons bilaterally in EB patients. Hyperactivity in the thalamus may be related to the primary cause of compensatory mechanism of EB sharing the common pathophysiological mechanism to other types of focal dystonia.

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