Subtraction Brain SPECT Imaging in a Patient With Paroxysmal Exercise-Induced Dystonia

Role of the Primary Somatosensory Cortex

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Background: Paroxysmal exercise-induced dystonia is a rare hyperkinetic disease characterized by episodic dystonic attacks after prolonged exercise. However, its pathophysiological and anatomical basis are poorly understood.

Objective: To explore the exact anatomical location responsible for paroxysmal exercise-induced dystonia by conducting ictal-interictal single-photon emission computed tomography subtraction, which was coregistered to the patient’s own magnetic resonance image.

Design: This is a case report of a 16-year-old boy who developed a right foot dystonic attack following prolonged exercise.

Result: Subtraction single-photon emission computed tomographic imaging showed significantly increased cerebral perfusion in the medial aspect of the postcentral gyrus and mildly increased perfusion in the primary motor area and cerebellum during an attack of foot dystonia.

Conclusions: The primary somatosensory cortex may be a relevant structure in paroxysmal exercise-induced dystonia. Paroxysmal exercise-induced dystonia may result from defective processing of sensory information.

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PAROXYSMAL EXERCISE-INDUCED DYSTONIA (PED), one of the 4 main categories of paroxysmal dyskinesia, is a rare hyperkinetic movement disorder that was first described by Lance in 1977. Paroxysmal exercise-induced dystonia is characterized by an episode of dystonic attack after prolonged muscular exertion, and each episode usually lasts for 5 to 30 minutes. The pathophysiological and anatomical basis of PED remains poorly understood. Perfusion studies during ictal events are an effective way to identify physiologically relevant structures.

To our knowledge, only one report has been published about the perfusion pattern during dystonic attacks in patients with PED. Kluge and colleagues demonstrated that dystonic attacks were accompanied by frontal hypoperfusion and cerebellar hyperperfusion in brain single-photon emission computed tomography (SPECT). However, the method of analyzing the perfusion pattern in their study was semiquantitative, using region of interest analysis, which cannot identify the precise structure other than the region of interest. In this study, we conducted ictal-interictal SPECT subtraction in a patient with PED to identify the anatomical structure that may be relevant to the pathophysiological features of PED.

REPORT OF A CASE

A 16-year-old boy presented with a 10-year history of stereotypic episodes of involuntary movement in his right foot after prolonged exercise. He first noticed gait difficulty due to involuntary movements in his right foot after prolonged walking during an elementary school excursion. The attack of involuntary movements was mostly precipitated by prolonged exercise, such as basketball, football, or bicycling. These attacks occurred 1 or 2 times a month, and the duration and frequency of dystonic attacks did not change for 10 years. Because he knew the precipitating factor, he usually avoided prolonged activities. His developmental milestones were normal, with no history of other neurological diseases. His 40-year-old father had a history of similar episodic involuntary movements of his legs after prolonged exercise in his adolescence, although these involuntary movements disappeared after adulthood.
The results of the neurological examination during the interictal state was normal. During an attack after 30 minutes of walking, his right foot was inverted and his big toe was dorsiflexed, compatible with dystonia (a video is available at http://www.archneurol.com). The dystonic attack in the right foot lasted for 15 to 30 minutes and did not propagate to other body parts. During the attacks, he sometimes had a slight feeling of stiffness within the affected foot. Dystonic attacks were mostly precipitated by prolonged walking or bicycling, but bicycling movements on supine position did not provoke an attack. Emotional stress and sensory stimuli did not trigger attacks. Sitting on a chair or distracting his attention (watching television or reading a book) during attacks decreased the duration of dystonia. His father also showed no neurological abnormalities.

The results of cerebral magnetic resonance imaging (MRI) and angiography were normal. Intercital and ictal electroencephalography showed no epileptiform discharges. Carbamazepine, 200 mg, markedly decreased the amplitude and duration of his dystonic attacks during 3 provocation tests; however, the patient did not respond to levodopa. With an intermittent introduction of carbamazepine before prolonged exercise, he now does not complain of dystonic attacks.

METHODS

SPECT STUDIES

After an intravenous dose of 99mTc-ethyl cysteinate dimer, SPECT images were obtained using a triple-head γ camera equipped with fan beam collimators (Multi-SPECT III; Siemens Medical Systems, Inc, Hoffman Estates, Illinois). The data were acquired in a 128 × 128-byte matrix over 360°, with 120 views obtained at 3° intervals using a circular orbit. The first (interictal) SPECT image was undertaken while the patient was lying on a bed with his eyes closed. For the second (ictal) SPECT image, injection of the radiotracer was performed during a dystonic attack. To induce a dystonic attack, we asked the patient to walk around a ward until foot dystonia developed. Approximately 2 minutes after right foot dystonia had emerged, we let the patient lie on a bed with his eyes closed and then injected approximately 0.02 Ci (740 MBq) of 99mTc-ethyl cysteinate dimer via an intravenous line in his left forearm for 1 minute. The patient continued to experience a dystonic attack on his right foot during and after radiotracer injection.

For comparison with voluntary contraction, we commanded the patient to perform dorsiflexion and inversion of his right foot on supine position for 5 minutes and then injected 99mTc-ethyl cysteinate dimer via an intravenous line in his left forearm. Subtraction SPECT imaging was obtained by subtracting images taken in the resting state from those taken during a dystonic attack and voluntary contraction using a computer program (SISCOM, Dayton, Ohio) implemented with SPM’99 software (Wellcome Department of Cognitive Neurology, London, England) and then superimposed on the standard T1-weighted structural MRI. A 20% increase in 99mTc-ethyl cysteinate dimer uptake was regarded as significant.

IMAGE PROCESSING FOR COREGISTRATION OF SPECT AND PATIENT’S MRI

Coregistration of SPECT and MRI was processed on an offline workstation (SUN Ultra 1 Creator Workstation; SUN Microsystems, Inc, Santa Clara, California) with the aid of a commercially available image analysis software package (ANALYZE 7.0; Mayo Foundation, Rochester, Minnesota). The SPECT subtraction procedure consisted of the following steps: ictal-interictal SPECT registration, normalization of radioisotope uptake level, and patient MRI-subtracted SPECT registration. Ictal hyperperfusion of subtracted SPECT was considered significant only when the regional cerebral blood flow difference in each pixel of the brain SPECT image was greater than 2 SDs.

RESULTS

Subtraction SPECT imaging (ictal–interictal) showed increased uptake of 99mTc-ethyl cysteinate dimer in the medial aspect of the postcentral gyrus (Figure 1). For more detailed anatomical localization, subtraction SPECT imaging was conducted with coregistration with the patient’s MRI. The result revealed that the 20% increased area of 99mTc-ethyl cysteinate dimer uptake in the subtraction SPECT image corresponded to the primary somatosensory cortex area, predominantly involving the left side of the postcentral gyrus. In addition, increased hyperperfusion was noted in the bilateral primary motor cortex and right side of the cerebellum (Figure 2A-C). No significantly increased or decreased uptake of 99mTc-ethyl cysteinate dimer was observed in other brain areas.

In a subtraction SPECT study during voluntary contraction, there were no brain areas showing significant changes of cerebral perfusion during voluntary foot contraction (Figure 2D).

COMMENT

Dystonia in PED has a long duration of attacks developed by ongoing exertion, occurs only after 10 to 15 minutes of prolonged exercise, and usually involves the body part being exercised, whereas dystonic attacks in paroxysmal kinesigenic dystonia occur immediately on movement. Recently, Wu and Jankovic5 reported 5 cases of adult-onset focal dystonia involving mainly the proximal lower limbs, occurring initially during long-distance running. Although the initial symptoms in runner’s dystonia were similar to our case, our patient showed a static course without shortening the duration of provocation time, childhood onset, and no associated tremor. Accordingly, the clinical characteristics in our patient were compatible with PED.

Subtraction SPECT imaging demonstrated significantly increased cerebral perfusion in the region of the primary somatosensory cortex area and mildly increased cerebral perfusion in the region of the primary motor area and cerebellum during an attack of foot dystonia, which suggests that increased cerebral perfusion in these areas may be responsible for the genesis of dystonia induced by prolonged exercise.

In this study, we obtained subtraction SPECT images using a computer program to overcome the problem of manually placing the region of interest, which can result in observer bias and large areas of the brain left unexplored. To improve the anatomical resolution of the subtraction SPECT image, we additionally coregistered...
the subtracted SPECT image with the patient’s MRI. This is likely why the perfusion pattern in our study was different from that found in the previous report by Kluge et al., in which dystonic attacks in patients with PED were associated with decreased frontal perfusion in addition to increased cerebellar perfusion.

Ictal SPECT imaging may reflect cerebral activation patterns during the maximum expression of the attack. The ictal perfusion pattern in our study demonstrated that foot dystonia induced by prolonged exercise was clearly associated with an increased cerebral perfusion in the somatotopical foot area of the primary somatosensory cortex, suggesting the primary somatosensory cortex as a relevant structure in PED. Although dystonia is generally considered to be a motor disorder, recent clinical and neurophysiologic studies support the concept that abnormal sensory processing may be relevant to the pathogenesis of focal dystonia. Dysfunction in the sensory system, such as impaired temporal or spatial discrimination, has been described in focal dystonia. Physiological studies in patients with dystonia have demonstrated abnormal inhibitory integration of afferent inputs or reduced motor cortical inhibition, contributing to an abnormal motor output. In focal dystonia, disruption of the normal homuncular arrangement in the somatosensory cortex of the affected hand seems to occur. Interestingly, functional neuroimaging studies have demonstrated increased patterns of metabolism in the primary somatosensory cortex during dystonic attacks, supporting the role of the primary sensory cortex and the processing of sensory information in the pathogenesis of focal dystonia. Regarding the change of cerebral perfusion in the bilateral somatosensory area in our patient, bilateral abnormalities of somatotopic organization in the primary somatosensory cortex and putamen have been reported in unilateral task-specific focal dystonia, supporting the notion that both hemispheres are originally, possibly genetically, affected by the disease. As a result, we postulate that increased function in the somatosensory cortex in PED could disrupt and influence processing of sensory information from the peripheral sensory system, which is provoked by prolonged exercise and ultimately results in dystonia.

Activation of the primary motor cortex and cerebellum is frequently observed during dystonic attacks in patients with focal dystonia. Overactivity in the primary somatosensory cortex and cerebellum has been reported in patients with focal dystonia. The increased activity in the primary motor cortex and cerebellum may contribute to the development and maintenance of dystonic movements.
matosensory cortex may influence motor neurons in the primary motor cortex through corticocortical connections.\textsuperscript{10} Cerebellar overactivity may reflect the increased work of cerebellar circuits confronted with distorted maps and their attempts to redesign the motor program to overcome the dystonic attack.\textsuperscript{15} Thus, mildly increased perfusion in the primary motor cortex and cerebellum, where regional cerebral blood flow difference in each pixel of the brain SPECT images was greater than 2 SDs, could be secondary.

It seems unlikely that the perfusion changes in our patient were merely exercise related or a postexercise effect because we undertook the ictal SPECT while the patient was lying down. Increased perfusion changes in the sensorimotor area during exercise were normalized to baseline after discontinuation of exercise.\textsuperscript{16} Considering no significant changes of cerebral perfusion during voluntary foot contraction, it is unlikely that increased perfusion was not caused by voluntary foot contraction itself. It is possible that the hyperperfusion in the somatosensory area may be involved in the abnormal sensation in the affected foot because the patient sometimes had a slight feeling of stiffness within the foot during dystonic attacks.

The limitation of our study is that it is a case report and the number of PED cases investigated by SPECT is

Figure 2. Subtraction single-photon emission computed tomographic (SPECT) imaging coregistered to magnetic resonance imaging revealed significantly increased cerebral perfusion in the region of the primary somatosensory cortex area and mildly increased perfusion in the region of the primary motor area and cerebellum during the attack of foot dystonia (A, horizontal imaging; B, coronal imaging; and C, sagittal imaging). During voluntary contraction of the right foot, there were no brain areas showing significant changes of cerebral perfusion in the subtraction SPECT image (D). L indicates left side.
too limited to draw any firm conclusions. Also, the ictal SPECT scan in our study may reflect brain activity associated with maintenance of dystonic posturing, but it sheds no light on the question of where dystonic posturing is initiated in the brain. Nevertheless, SPECT findings of hyperperfusion in the primary somatosensory region during a dystonic attack without significant perfusion changes during voluntary contraction suggest that this area may play an important role in the development of dystonia in a patient with PED.

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