Regional Cerebral Blood Flow Response in Gray Matter Heterotopia during Finger Tapping: An Activation Study with Positron Emission Tomography

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Summary: We examined regional cerebral blood flow response in a patient with gray matter heterotopia located beneath the sensorimotor cortex during a finger tapping task. We found regional cerebral blood flow was specifically increased during contralateral finger tapping. This indicated the possibility of functional differentiation of the ectopic neurons despite incomplete migration.

Index terms: Brain, abnormalities and anomalies; Cerebral blood flow; Positron emission tomography

Heterotopic gray matter is a cluster of abnormally isolated neurons located in the subcortical or deep white matter (1, 2). It usually manifests as variable developmental delay of the brain (3) and seizures (4). Although the morphological characteristics and relationship to developmental and neurologic manifestations have been extensively studied with magnetic resonance (MR) imaging (2–8), it is still unknown whether this entity is related to the execution of specific brain functions. We investigated the blood flow response of ectopic gray matter during physiological task loading using positron emission tomography (PET) with oxygen-15-labeled water.

Case Report

A 20-year-old college student who was neurologically and mentally normal but who had onset of tonicoclonic seizures at age 19 was examined. The gestation period and birth had been uncomplicated. MR images showed multiple nodular ectopic gray matter below the right inferior frontal gyrus and below the right and left precentral and postcentral gyri (Fig 1A and B). All nodules were isointense with the cortical gray matter on both T1-weighted and T2-weighted images. No abnormal contrast enhancement was observed after intravenous administration of gadopentetate dimeglumine. Polymicrogyria was found in the left parietal lobe and right frontal lobe. In addition, associated agenesis of the septum pellucidum was noted.

Regional cerebral blood flow (CBF) was measured by means of PET with oxygen-15-labeled water during tapping of the right fingers, the left fingers, and resting. Motor tasks were chosen because some clusters of heterotopic gray matter were located beneath the sensorimotor cortices bilaterally. In the tapping task, the thumb was repeatedly touched against the tip of the index finger, the middle finger, the ring finger, and the little finger in this order and then in the reverse order at a self-paced rate of 1 Hz.

Oxygen-15-labeled water (1110 MBq/5 mL) was administered intravenously as a bolus 30 seconds after the patient was asked to initiate the motor task. PET scanning was started when the tracer was first observed in the brain and was continued for 90 seconds. After the decay of oxygen-15-labeled water (physical half-life = 123 seconds), the next measurement sequence could be initiated. The absolute CBF value for the resting trial was calculated by the method developed by Herscovitch et al (9) and Raichle et al (10). The procedure was described in detail elsewhere (11). The mean whole-brain CBF determined by the method described by Fox and Raichle (12) was estimated to be 45 mL/100 mL per minute in this patient. For the finger-tapping trials, PET images were normalized to the whole-brain blood flow of 45 mL/100 mL per minute under the assumption that there was no change of global CBF between resting and finger-tapping trials (13).

The absolute CBF value of the heterotopia below the right inferior frontal gyrus was 50.1 mL/100 mL brain per minute at rest. The CBF during right and left finger tapping was 50.6 and 49.1 mL/100 mL per minute, respectively.

The mean CBF for cortical gray matter, basal ganglia, and white matter was 54.9 mL/100 mL per minute, 62.3 mL/100 mL per minute, and 25.0 mL/100 mL per minute,

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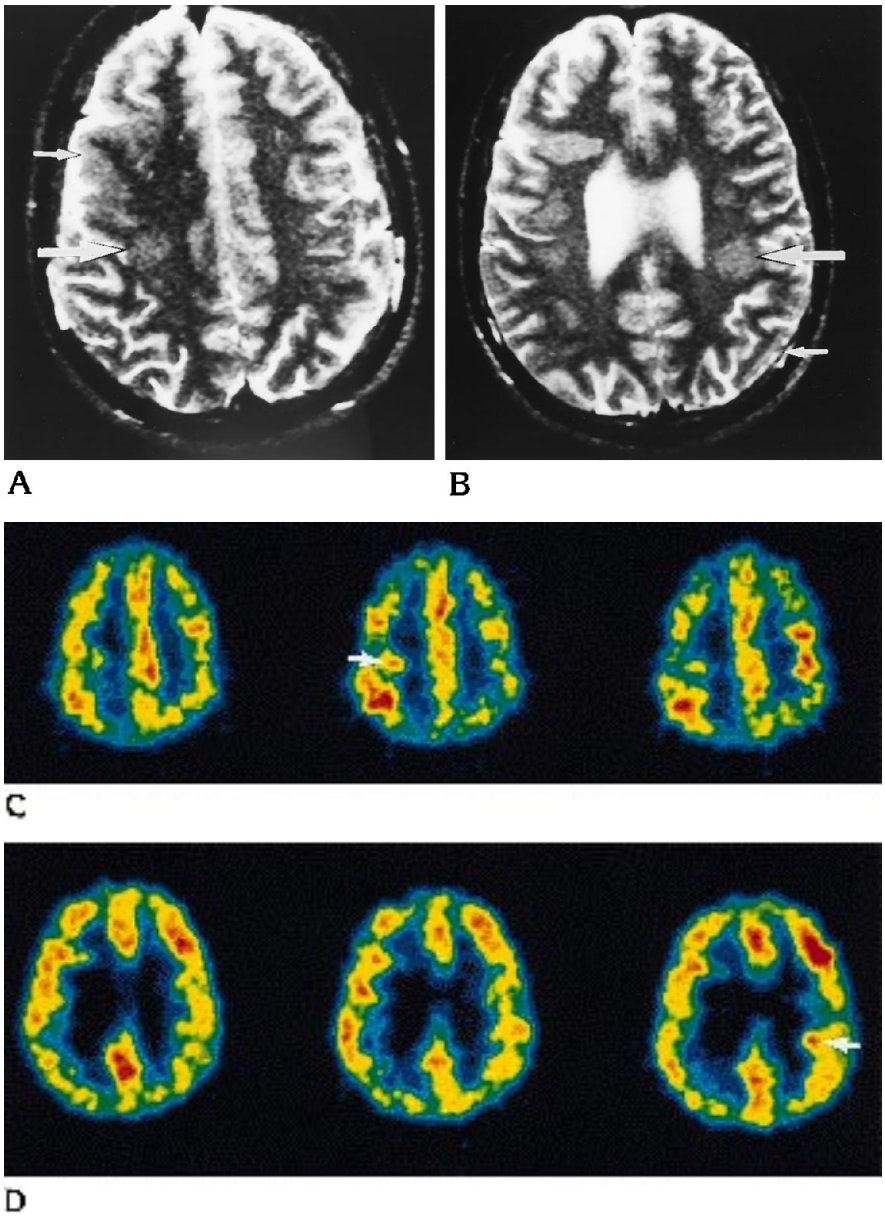

Fig 1. *A* and *B*, Multiple nodules of subcortical heterotopic gray matter are seen on T2-weighted MR images (3000/90 [repetition time/echo time]). *Large arrows* indicate the ectopic gray matter below the right (*A*) and the left (*B*) sensorimotor cortex. Abnormal gyration is indicated by *small arrows*. *A* and *B* were obtained at 51 mm and 45 mm, respectively, above and parallel to the AC-PC line.

C, Regional cerebral blood flow images acquired 51 mm above the AC-PC line during resting (*left*), left finger tapping (*center*), and right finger tapping (*right*) tasks. The subcortical ectopic gray matter beneath the right sensorimotor cortex was specifically activated during the left finger tapping task, as indicated by the *arrow*. The AC-PC line in the PET measurement was identified while the patient was lying on the bed for the PET study as follows: a lateral cranial radiograph was taken with a metal line landmark placed parallel to the scanning sections, and the tilting angle of the PET gantry was determined by fitting the cranial radiograph to the midsagittal MR image and by measuring the angle produced by the metal line landmark and the AC-PC line of the MR image.

D, Regional cerebral blood flow images acquired 45 mm above the AC-PC line during resting (*left*), left finger tapping (*center*), and right finger tapping (*right*) tasks. The subcortical heterotopic gray matter beneath the left sensorimotor cortex was specifically activated during the right finger tapping task, as indicated by the *arrow*. Blood flow of ectopic gray matter in the right hemisphere did not change during the finger tasks.

respectively. The CBF of polymicrogyria in the right frontal lobe and left parietal lobe was 50.2 mL/100 mL per minute and 54.3 mL/100 mL per minute, respectively.

CBF images acquired at 51 mm above and parallel to the anterior commissure–posterior commissure (AC-PC) line are shown in Fig 1C. The heterotopia below the right sensory-motor cortex showed a blood flow rate of 53.3 mL/100 mL per minute in the resting condition (left-sided image in Fig 1C). During left finger tapping, the blood flow of the heterotopia was increased by 18% (center image, indicated by an arrow). Right finger tapping did not increase the blood flow of this heterotopic gray matter (right-sided image). Fig 1D shows CBF images acquired at 45 mm above and parallel to the AC-PC line during resting (left-sided image) left finger tapping (center image), and right finger tapping (right-sided image). The blood flow rate of the heterotopia below the left sensory-motor cortex was 51.9 mL/100 mL per minute at rest and was specifically increased by 20% during right finger tapping (indicated by an arrow in the right-sided image in Fig 1D). The CBF for the overlying sensorimotor cortex in the left hemisphere was 51.2 mL/100 mL per minute during resting and increased by 18% during right finger tapping.

Discussion

Gray matter heterotopia results from incomplete migration of neurons during brain development, when neurons are generated in proliferative zones situated along the ventricular surface and then migrate along radially oriented

glial cells to their final position in the cortex (14).

There are several reports of the study of the perfusion of gray matter heterotopia with the use of single-photon emission CT and technetium-99m hexamethylpropylenamine oxime (^{99m}Tc-HMPAO) and of the study of the glucose metabolic rate by means of PET with fludeoxyglucose F 18. These studies found perfusion of nodular (15) and laminar heterotopia (16) identical to or increased compared with that of the overlying cortical mantle. Bairamian et al reported their findings in a 33-year-old man who had a lifelong history of seizures and psychomotor retardation (17). The glucose metabolism of the heterotopia seated in the right centrum semiovale was identical to that of the normal frontoparietal cortex of the left hemisphere. Calabrese et al (18) measured the cerebral metabolic rate of glucose in a 21-year-old left-handed medical student who had heterotopia in the left temporoparietal and left frontal regions. The subject showed normal intelligence but selective deficits of verbal fluency and spatial-figural relationships. These researchers observed a glucose metabolic rate of heterotopia equivalent to that of the cortical regions and twofold greater than that of corresponding subcortical white matter of the right hemisphere. In our patient, the CBF values of the heterotopia were the same as the mean cortical CBF and twice that of the white matter in the resting condition. These studies indicate that the blood flow and metabolic activity of ectopic gray matter are identical to those of the normally laminated cortical gray matter in the resting condition.

Neural activation is usually associated with an increase of local CBF and glucose metabolism (19). The brain regions responsible for certain functions have been elucidated by comparing the blood flow or glucose metabolic rate during task loading with that during the non–task loading state. In our patient, during unilateral finger tapping, the blood flow of heterotopia below the contralateral sensory-motor cortex was specifically increased. The magnitude of increase was 18% in the right hemisphere and 20% in the left hemisphere. In healthy volunteers, Shibasaki et al (20) found a 22% and 20% increase in the contralateral precentral gyrus and postcentral gyrus, respectively, during the same motor task as used in the present study. Therefore, the magnitude of blood flow response of heterotopias in our patient was equivalent to that in the normally laminated sensorimotor area in healthy volunteers. These observations suggest that the heterotopia below the sensorimotor cortices in our patient might be connected with the rest of the brain and functionally activated.

Calabrese et al (18) studied metabolic response during a verbal fluency test and found a 21% increase in the heterotopia located in the left temporoparietal cortex. However, the left temporal cortex overlying the heterotopia was hypometabolic in the resting condition, and only a 1% increase was found during a verbal fluency task. Instead, they observed a strong activation of the Broca and Wernicke areas of the right hemisphere. Because their patient showed normal language function and superior intelligence, they speculated that a compensation mechanism for the left hemisphere heterotopia operative during brain development had prevented severe neuropsychological abnormality and mental retardation in their subject. On the other hand, the heterotopia in our patient was bilateral, and motor function was normal. The sensorimotor cortices overlying the heterotopia showed a blood flow increase of 20%, which corresponded to that of a normally laminated sensorimotor cortex in healthy volunteers. The difference between our patient and that of Calabrese et al (18) indicates that the formation of appropriately laminated cortices and their functional differentiation may be a primary factor affecting the severity of deficits. Barkovich and Kjos (5) observed that an anomalous overlying cortex is significantly correlated with degree of developmental delay. Livington and Aicardi (6) described two patients who had mild clinical symptoms and bilateral thin-band heterotopia with a normal-appearing overlying cortex. Our results accord well with these studies in that the effect of migration disturbance on cortical development is suggested to have an important effect on the clinical manifestations.

It is still unknown whether the heterotopia below the sensorimotor cortices in our patient included the pyramidal neurons directly projecting to the spinal cord. There are several reports of experimental studies of the projection of heterotopic pyramidal neurons to spinal cord. Jensen and Killackey (21) produced periventricular ectopic neurons in the adult rat by prenatal irradiation and studied the projection of ectopic neurons on the basis of the retrograde

axonal transport of horseradish peroxidase (HRP) after its injection into the spinal cord. When HRP was injected into the spinal cord in healthy rats, corticospinal tract neurons retrogradely labeled after HRP injection were situated only in layer V of the cerebral cortex. In the irradiated rat, retrogradely labeled neurons were found in the periventricular heterotopias. Terashima et al (22) examined a recessive mutation in reeler mice that produces abnormalities of laminar organization in the cerebral and cerebellar cortices. In the reeler mice, the labeled corticospinal neurons after injection of HRP into the spinal cord were scattered diffusely throughout all levels of the corresponding cortical area. These studies indicate that in the rat and mice neither appropriate location nor laminar organization is essential for projection of pyramidal neurons to their target region. Therefore, there is a possibility that heterotopic neurons below the sensorimotor cortex in our patient also project to the spinal cord and directly participate in the execution of contralateral motor tasks.

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