

## Hemidystonia, Hemichorea, and Motor Aphasia Associated With Bilateral Ischemic Lesions in the Striatum: Regional Cerebral Blood Flow Studies To Clarify the Pathophysiology

The physiologic mechanisms of dystonia and chorea are not fully understood. The sudden appearance of involuntary movements is usually attributed to a vascular lesion in the contralateral basal ganglia.<sup>1</sup> Involuntary movements of vascular origin are particularly interesting because the lesions may be more localized than those of metabolic or anoxic origin, thus permitting speculation on the pathophysiology.

Brain function imaging, using positron emission tomography (PET) and single photon emission computed tomography (SPECT), is well suited for studying cerebral blood flow and neuronal activity. *N*-isopropyl-*p*-[<sup>123</sup>I] iodoamphetamine (<sup>123</sup>I-IMP), a brain perfusion imaging agent, can show temporal changes in the distribution patterns of the brain.<sup>2-4</sup> Immediately after injection, the lungs accumulate almost 100% of IMP.<sup>5,6</sup> Thereafter, the lungs act as a reservoir of IMP for the input to the brain for a long period postinjection.<sup>7</sup> Early IMP images (15 to 30 min postinjection) show excellent correlation with regional cerebral blood flow.<sup>4</sup> Late IMP images (180 to 300 min postinjection) frequently show a "redistribution" phenomenon that is characterized by the filling-in of the tracer in the hypoperfused areas observed in the early images.<sup>7</sup> Nishizawa and collaborators believed that this redistribution phenomenon is related to metabolic activity in the viable cerebral tissue.<sup>4</sup>

The purpose of this case report is to study the regional cerebral blood flow and neuronal activity, using <sup>123</sup>I-IMP brain SPECT, of a child with hemidystonia, hemichorea, and motor aphasia associated with bilateral ischemic lesions of the striatum in order to clarify the pathophysiology. It is hypothesized that the motor aphasia was associated with cortical deactivation induced by the ischemic lesions in the striatum or the striatum lesions.

### Case Report

In January 1995, a previously healthy 5-year-old girl was admitted because of right hemiparesis. She was born at term to healthy unrelated parents following a normal pregnancy. Birthweight was 3210 g. The neonatal period was uneventful. Her developmental milestones were normal; she walked at 9 months and talked at 13 months. Four months before admission, the parents noted that she had difficulty walking due to a tendency to catch her right foot followed a few weeks later by clenching the right hand. There was no history of trauma, recent immunization, or recent viral infection. Neurologic examination revealed dystonic spasms of the right upper and lower limbs without torsion of the neck and trunk. At that time, there were no abnormal movements in the left upper and lower limbs. There were no motor weakness or sensory disturbances. Deep tendon reflexes were normal. She was discharged 1 month later with persistent right hemidystonia while aspirin was administered to prevent a recurrence of ischemic attack. Five months later, in July, she was readmitted because of involuntary movements of the left upper and lower limbs and aphasia. Neurologic examination revealed constant, involuntary, purposeless, and non-rhythmic movements in the left upper and lower limbs; the right hemidystonia remained unchanged. Although her psychomotor development was normal, she had marked speech impairment: expressive language skills were impaired while receptive language skills were normal. There was hyperflexion of the right elbow, wrist, and fingers with adduction of the wrist. The right arm had a tendency to retropulsion-abduction with elevation of the shoulder. The right lower limb was held in hyperextension and internal rotation with inversion and plantar flexion of the foot. The left upper and lower limbs were

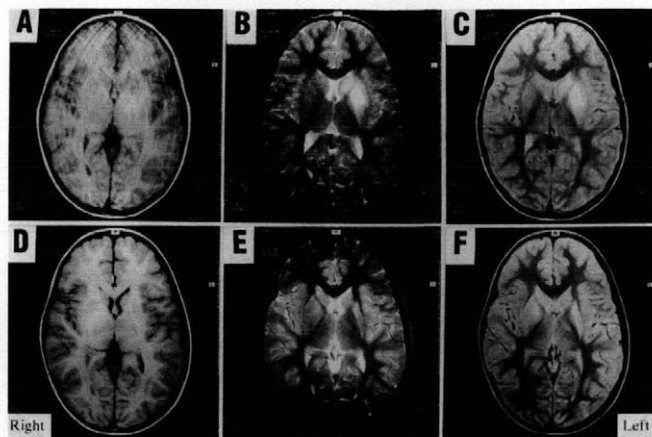


Figure 1. Cranial MRI performed in January 1995 (A, B, and C), ischemic lesions were shown in the head of the left caudate nucleus and the left putamen at a time when the patient exhibited right hemidystonia. Cranial MRI from July 1995 (D, E, and F), additional ischemic lesions were shown in the right striatum and the left putamen showed marked atrophy at a time when the patient exhibited left hemichorea and motor aphasia as well as right hemidystonia.

in constant choreiform movements. The abnormal posture and movements disappeared during sleep and were aggravated by psychogenic stress and voluntary movements.

The D dimer level was elevated at 5.3 mg/mL (normal range, 0.0–0.5 mg/mL). Additional coagulation studies including prothrombin time, activated partial thromboplastin time, fibrinogen, proteins C and S, and antithrombin III levels, as well as lupus anticoagulant and anticardiolipin antibodies were normal. Lactate and pyruvate levels in the blood and cerebrospinal fluid were not elevated (blood: lactate 5 mg/dL and pyruvate 0.6 mg/dL; cerebrospinal fluid; lactate 13 mg/dL and pyruvate 1.1 mg/dL). An electrocardiogram and an echocardiogram were also normal.

Cranial magnetic resonance imaging (MRI) was obtained with 1.5 Tesla magnetic resonance unit (Siemens, Magnetom) in the axial sections using spin echo sequences of  $T_R = 600$  msec/ $T_E = 15$  msec for  $T_1$ -weighted images,  $T_R = 3500$  msec/ $T_E = 93$  msec for  $T_2$ -weighted images, and  $T_R = 3500$  msec/ $T_E = 19$  msec for proton density weighted images. An initial MRI was performed in January 1995 while the right upper and lower limbs exhibited dystonic spasms (Figure 1A, B, and C).  $T_2$ -weighted images and proton density weighted images showed increased signal intensity lesions involving the left caudate nucleus and the left putamen, whereas  $T_1$ -weighted images showed decreased signal intensity. A second MRI was performed in July following the right hemidystonia, left hemichorea, and motor aphasia (Figure 1D, E, and F). On  $T_2$ -weighted images and proton density weighted images, increased signal intensity lesions were shown not only in the left putamen but also in the right caudate nucleus and the right putamen; the left putamen showed marked atrophy. On both MRIs, there were no cerebellar abnormalities. Carotid angiogram did not show any narrowing or obstruction of the cerebral blood vessels.

Haloperidol (0.5 mg twice daily, from the second episode onward) diminished the choreiform movements. On the other hand, levodopa, diazepam, and dantrolene sodium did not affect the dystonia. The motor aphasia gradually improved spontaneously. At 16-month follow-up, the patient demonstrated severe hemidystonia affecting the right upper and lower limbs; the choreiform movements were absent and she could speak fluently.

### Methods

Ten control subjects, aged 3 to 9 years old with a mean  $\pm$  SD of  $6.8 \pm 2.1$  years, were selected from children who had <sup>123</sup>I-IMP brain SPECT studies between 1993 and 1994 for evaluation of suspected neurologic problems not accompanied by motor dysfunction or MRI abnormalities, because radioactive tracer could not be injected into normal children due to ethical considerations.

**Table 1. Normalized Average Pixel Values\* From the Patient and the Controls**

	Frontal Cortex		Parietal Cortex		Temporal Cortex		Basal Ganglia		Cerebellar Cortex	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
<b>Patient</b>										
1st study (January 1995)										
Early <sup>†</sup>	0.93	1.07	0.99	1.07	0.90	0.99	0.84	1.04	0.98	0.99
Late <sup>‡</sup>	0.86 <sup>§</sup>	1.03	0.99	0.99	0.97	1.06	0.89 <sup>§</sup>	1.03	0.93	1.07 <sup>  </sup>
2nd study (July 1995)										
Early	0.91	0.97	1.05	1.00	0.84	0.82	0.83	0.88	0.98	0.97
Late	<b>0.99</b>	<b>1.10</b>	1.03	1.04	0.98	1.04	0.97	1.07	0.92	1.04
<b>Controls (n = 10)</b>										
Early mean	1.02	1.03	1.06	1.06	0.94	0.99	0.87	0.84	0.89	0.89
SD	(0.07)	(0.07)	(0.05)	(0.04)	(0.06)	(0.08)	(0.09)	(0.08)	(0.07)	(0.07)
Late mean	1.03	1.03	1.04	1.05	0.98	1.00	1.01	1.03	0.96	0.98
SD	(0.06)	(0.07)	(0.04)	(0.09)	(0.06)	(0.06)	(0.05)	(0.05)	(0.04)	(0.04)

\*Regional average values/average values of occipital cortices.

<sup>†</sup>Data obtained 20 min postinjection.

<sup>‡</sup>Data obtained 300 min postinjection.

<sup>§</sup>Below the lower boundary of the 95% confidence interval.

<sup>||</sup>Beyond the higher boundary of the 95% confidence interval.

SPECT scans were performed using a Hitachi SPECT 2000 H-40 equipped with high resolution collimators. The subjects received intravenous injection of <sup>123</sup>I-IMP followed by SPECT scans 20 min and 300 min postinjection. The patient was sedated with chloral hydrate; her involuntary movements were completely abolished during the scans but the involuntary movements continued during a period between early and late SPECT scans. Four of the control subjects were also sedated with chloral hydrate. Acquisition data were collected using 64 total steps of 15 sec each into a 64 × 64 matrix yielding a pixel size of 4.0 mm, and axial, sagittal, and coronal images with 8.0 mm-slice thickness were reconstructed. Computer-automated square regions of interest (16.8 mm × 16.8 mm) were created over the frontal, parietal, temporal, and occipital cortices, basal ganglia, and

cerebellar hemispheres. The cerebellar values in the patient were significantly different between the left and right sides. Therefore, the average pixel value in each region of interest was normalized to occipital value without a significant difference between the left and right sides. The patient's region of interest data were compared to the control subjects.

### Results

Results of the region of interest analyses are shown in Table 1. The first SPECT study (Figure 2) for the patient was performed in January 1995 when the patient exhibited right hemidystonia and an ischemic lesion in the left striatum on MRI. Early images obtained 20 min postinjection showed hypoperfused areas both in the left basal ganglia and in the left frontoparietal lobes. Late images

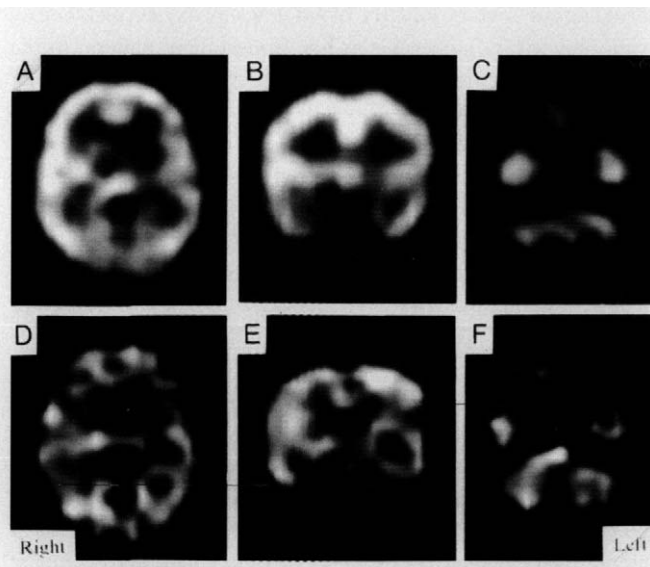


Figure 2. SPECT performed in January 1995. Axial (A and D) and coronal (B and E) sections through the basal ganglia and axial sections (C and F) through the cerebellum are shown. Early images (A, B, and C, 20 min postinjection) showed hypoperfused areas in the left basal ganglia and the left frontoparietal lobes. Late images (D, E, and F, 300 min postinjection) did not show redistribution in the hypoperfused areas observed on the early images. The cerebellar vermis and the right hemisphere showed hyperperfusion on the late images, whereas the early images showed equal cerebellar perfusion.

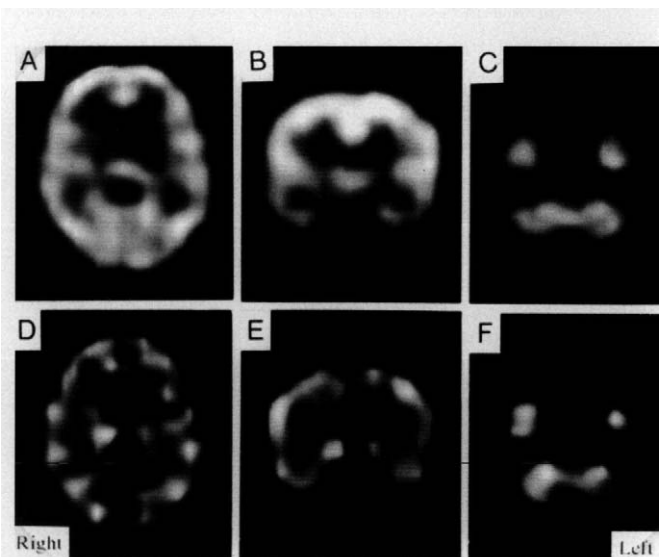


Figure 3. SPECT performed in July 1995. Early images (A, B, and C) showed hypoperfused areas in the basal ganglia bilaterally. Late images (D, E, and F) showed redistribution in the right basal ganglia but not in the left basal ganglia. The left frontal lobe was hypoperfused. The right cerebellar hemisphere was hyperperfused.

obtained 300 min postinjection did not show a redistribution in the hypoperfused areas observed in the early images. The right cerebellar hemisphere showed hyperperfusion on the late images, while the early images did not show any significant difference between the right and left hemispheres.

The second SPECT study (Figure 3) was performed in July 1995 when the patient exhibited the right hemidystonia, the left hemichorea, and motor aphasia and the MRI showed ischemic lesions in the right striatum as well as in the left putamen. On the early images, the left basal ganglia and the left frontal lobe showed hypoperfusion, although the normalized average pixel values were not below the lower boundary of the 95% confidence interval from the controls. In addition, the perfusion in the right frontal lobe and the right basal ganglia decreased compared to the first study. These findings were consistent with the ischemic lesions in both striatum on the second MRI. Late images showed a redistribution in the right frontal lobe and the right basal ganglia, but not in the left frontal lobe and the left basal ganglia. The late right cerebellar hyperperfusion appeared to continue, although the normalized average pixel value was not beyond the higher boundary of the 95% confidence interval from the controls.

Control subjects' SPECT images did not show abnormal perfusion pattern; there was no asymmetrical perfusion in the cerebellum.

### Discussion

The incidence of ischemic stroke in children is estimated at 0.2 to 0.6 per 100,000 per year.<sup>8,9</sup> In approximately half of these patients, the ischemic events were confined to the basal ganglia.<sup>9</sup> In this patient, the asymmetry of the striatal lesions and the nonprogressive clinical course suggested that the lesions were caused by vascular events rather than any metabolic diseases. Although the angiogram did not show any narrowing or obstruction of the cerebral blood vessels, the elevated D dimer level indicated the presence of an intraluminal clot in the cerebral blood vessels. An intraluminal clot in the middle cerebral artery was most likely obstructing, in a transient fashion, the origin of the lateral lenticulostriate arteries because the ischemic lesions in the striatum were located in the supply areas of the lateral lenticulostriate perforating arteries. Kappelle and collaborators reported that the cortical supply areas of the middle cerebral artery are often saved from ischemia by collateral blood supply from transcortical and transdural anastomoses, but not sufficiently for the deeper areas such as the basal ganglia.<sup>10</sup> This may explain why the MRI showed no abnormal signal intensity areas in the cortical regions in spite of the ischemic lesions in the striatum.

The patient developed right hemidystonia, left hemichorea, and motor aphasia associated with bilateral ischemic lesions in the striatum. Based on the clinical course and the neuroimages, the site of the lesion responsible for the hemidystonia is likely in the contralateral striatum. The lesion causing the hemichorea is also likely to be in the contralateral striatum. Previous studies have shown that basal ganglia infarcts may be involved in cognitive and behavioral dysfunctions as well as in motor dysfunctions.<sup>11,12</sup> Dominant-hemisphere putamen is associated with the activation and execution of movements to express already acquired language.<sup>13</sup> Speech disorders occurred in 25% of the patients with striatum lesions.<sup>12</sup>

Furthermore, it has been reported that small, deep ischemic lesions, as in a basal ganglia lacunae, produced ipsilateral cortical hypoperfusion, probably due to the interruption of the neural pathways.<sup>14</sup> In this patient, SPECT demonstrated hypoperfusion areas in the bilateral striatum and the left frontal lobe. Consequently, the motor aphasia in this patient may be associated with the cortical deactivation induced by the ischemic lesions in the striatum or the striatum lesions.

The lesions causing dystonia were in the contralateral striatum, especially in which the putamen was involved. Such putaminal lesions have been suspected to destroy both the direct striatopallidal pathways supporting cortically generated movement, and the indirect pathways via lateral globus pallidus and subthalamic nucleus that eventually inhibits thalamocortical excitation of premotor cortical areas.<sup>12</sup> Thus, the destruction of the direct pathways reduces cortically generated movement whereas the destruction of the indirect pathways increases thalamocortical drive. Abnormal interaction between direct and indirect pathways may explain the pathophysiology of the dystonia, of which prolonged co-contraction of agonist and antagonist muscles is characteristic.

The lesions causing choreiform movements were also in the contralateral striatum, which was involved less extensively compared to the lesions causing the dystonia. In Huntington's chorea, the striatal projection to the lateral pallidum is more severely affected.<sup>15</sup> Experimental hemichorea can be produced by the injection of  $\gamma$ -aminobutyric acid (GABA) antagonists into the lateral pallidum<sup>16</sup> or the subthalamic nucleus.<sup>17</sup> Thus, the involvement of indirect pathways via lateral globus pallidus and subthalamic nucleus would cause chorea. When the striatum is affected, the indirect pathways may be more vulnerable than the direct pathways.

PET studies have revealed several examples of functional depression induced in distant neuronal units by a localized lesion, including cases where both the blood flow and oxygen metabolism were reduced in the cerebellar hemisphere contralateral to the supratentorial infarcts.<sup>18</sup> This phenomenon of "crossed cerebellar diaschisis" is believed to be caused by a transneuronal degenerative process.<sup>19,20</sup> Similarly, supratentorial and contralateral cerebellar hyperperfusion (crossed cerebellar hyperperfusion) was reported in some patients with partial seizures during the ictal phase.<sup>21-23</sup> These phenomena have been ascribed to a functional connection between the cerebral cortex and the contralateral cerebellar hemisphere. The input of the cerebellum consists of two major circuits,<sup>24</sup> including the mossy fibers originating from the ipsilateral spinal cord and brainstem centers and the climbing fibers originating from the contralateral inferior olive. The inferior olive receives fibers ascending in the spinal cord and some fibers from higher brain centers. The output of the cerebellar hemisphere is primarily through the dentate nucleus and the fibers terminate in the red nucleus and lateral and ventral portions of the contralateral thalamus. Stated simply, the cerebellar hemispheres modulate limb movements of the ipsilateral side. In this patient, late IMP images revealed hyperperfusion in the right cerebellar hemisphere, contralateral to the left striatal lesion responsible for the hemidystonia, while early IMP images showed equal cerebellar perfusion. This may indicate that the right hemidystonia, appearing during a period between early and late SPECT scans, increased right cerebellar activity. Recent clinical and experimental investigations provide evidence that the

cerebellum may play a critical role in the pathophysiology of dystonia.<sup>25-27</sup> SPECT imaging study from a patient with dystonia indicated that there was asymmetry of regional cerebral blood flow in the deep cerebellar nuclei and cerebellar hemispheres.<sup>27</sup> In the genetically dystonic rat, the deep cerebellar nuclei fired more rhythmically than normal, suggesting abnormal Purkinje cell inhibition control.<sup>26</sup> The axons of Purkinje cells terminate in the deep cerebellar nuclei, where glucose utilization was significantly elevated in the dystonic rat in comparison with unaffected littermate controls.<sup>25</sup> Along with the notion that almost all cerebellar activity is inhibitory,<sup>24</sup> it is hypothesized that the increased cerebellar activity in this patient with dystonia was induced secondarily to suppress the prolonged co-contraction of agonist and antagonist muscles characteristic of dystonia. The SPECT findings in a single patient cannot, however, establish a role for the cerebellum in the pathophysiology of dystonia. This hypothesis needs to be confirmed by further studies.

Satoru Takahashi, MD  
Junichi Oki, MD  
Akie Miyamoto, MD  
Akimasa Okuno, MD  
*Department of Pediatrics  
Asahikawa Medical College  
Asahikawa, Japan*

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