Degeneration of the Ipsilateral Substantia Nigra Following Cerebral Infarction in the Striatum

Makoto Nakane, MD; Akira Teraoka, MD, DMSc; Reinin Asato, MD, DMSc; and Akira Tamura, MD, DMSc

Background and Purpose: In rats, degeneration of the ipsilateral substantia nigra occurs a few weeks after occlusion of the middle cerebral artery. The aim of this study was to clarify whether similar change is observed in stroke patients.

Methods: Eighteen patients with striatal infarction and six patients with cortical infarction in the territory of the middle cerebral artery were examined by means of sequential magnetic resonance imaging.

Results: In all patients with striatal infarction, T2-weighted images revealed a high-signal-intensity spot in the ipsilateral substantia nigra. Changes in the ipsilateral substantia nigra appeared at day 14 after stroke on average and then became less intense and smaller a few months after the stroke. By contrast, we observed no nigral changes in any patient with cortical infarction.

Conclusions: The degenerative change in the ipsilateral substantia nigra initially found in the rat model similarly occurred in patients with striatal infarction. This remote change in the substantia nigra may represent magnetic resonance imaging detection of neuropathologic changes in this region through the striatonigral pathway. (Stroke 1992;23:328–332)

KEY WORDS • cerebral infarction • magnetic resonance imaging • substantia nigra

It has been reported that focal cerebral ischemia can cause neuropathologic changes not only in the area of infarction, but also in certain distant, nonischemic areas remote from the original infarct.1–5 In rats, neuronal loss, gliosis, and atrophy of the ipsilateral substantia nigra occur approximately 2 weeks after occlusion of the middle cerebral artery (MCA).1 The neuronal degeneration of the ipsilateral substantia nigra may result from excessive excitation due to loss of an inhibitory γ-aminobutyric acid (GABA)ergic input as a result of infarction of the striatum. The aim of this study was to clarify whether similar change in the substantia nigra is observed in stroke patients. In clinical cases, there are a few autopsy reports of neuronal loss and atrophy in the ipsilateral substantia nigra after massive basal ganglia infarction.6–7 Therefore, we tried to detect change in the ipsilateral substantia nigra in cases of striatal infarction by means of magnetic resonance imaging (MRI).

Subjects and Methods

We selected 18 patients who had been admitted within 1 week after the onset of stroke, had a moderate to large infarct in the striatum with or without an adjacent cortical infarct, and were examined by MRI at the level of the substantia nigra (striatal infarction group). Six other patients who had a moderate to large infarct in the cerebral cortex of the MCA territory without a striatal infarct were selected as controls (cortical infarction group).

The MRI was performed on a 0.5-T magnetic resonance imager (Resona, Yokokawa Medical, Tokyo). In all cases, T1-weighted (repetition time 600 or 350 msec, echo time 30 or 15 msec) and multiecho T2-weighted (repetition time 2,000 msec; echo time 100 msec) axial and/or coronal images were obtained.

Results

In all patients of the striatal infarction group, T2-weighted images revealed a high-signal-intensity spot in the ipsilateral substantia nigra, probably more prominent in the pars compacta than in the pars reticulata (Table 1, Figures 1–3). This lesion was limited to the ipsilateral substantia nigra and was not observed in adjacent structures. This abnormal spot appeared an average of 14.3 days after the onset of stroke, except in case 9, in which the MRI was taken 5 months after the onset. This change was not observed on MRI films taken within 7 days (Figure 1, Figure 4). The change in the ipsilateral substantia nigra on MRI became less intense and smaller a few months later (Figure 3). The change in this area was not clear in T1-weighted images at any time.

In no patient of the cortical infarction group was any change observed in the ipsilateral substantia nigra on MRI films (Table 1).
TABLE 1. Clinical and MRI Findings in 18 Patients With Striatal Infarction and Six Patients With Cortical Infarction

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (yr)</th>
<th>Sex</th>
<th>Putamen</th>
<th>Caudate head</th>
<th>Globus pallidus</th>
<th>Cortex</th>
<th>Substantia nigra</th>
<th>Day of appearance</th>
<th>Days of MRI</th>
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<tbody>
<tr>
<td>1</td>
<td>66</td>
<td>M</td>
<td>+</td>
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<td>15, 1, 2, 5, 7, 15, 25, 43</td>
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<td></td>
<td>+</td>
<td>14, 2, 14</td>
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<tr>
<td>5</td>
<td>64</td>
<td>M</td>
<td>+</td>
<td>–</td>
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<td>15, 1, 2, 4, 9, 15, 29, 74; 6 months</td>
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<td>6</td>
<td>56</td>
<td>M</td>
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<td>8, 3, 19</td>
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<td>8</td>
<td>77</td>
<td>M</td>
<td>+</td>
<td>+</td>
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<td>15, 1, 2, 7, 15, 32; 6 months</td>
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<td>9</td>
<td>80</td>
<td>M</td>
<td>+</td>
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<td></td>
<td>+</td>
<td>5 months; 2, 5 months</td>
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<td>75</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>–</td>
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<td>+</td>
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<td>45</td>
<td>F</td>
<td>+</td>
<td>+</td>
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<td>–</td>
<td>+</td>
<td>11, 2, 3, 6, 11, 20, 31, 79; 4 months</td>
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<tr>
<td>16</td>
<td>78</td>
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<td>+</td>
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<td>83</td>
<td>M</td>
<td>+</td>
<td>–</td>
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<td>–</td>
<td>+</td>
<td>18, 7, 18</td>
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<tr>
<td>18</td>
<td>78</td>
<td>F</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>11, 2, 3, 7, 11, 21</td>
</tr>
</tbody>
</table>

MRI, magnetic resonance imaging; M, male; F, female. In putamen, caudate head, globus pallidus, and/or cortex: +, involved; −, not involved. In substantia nigra: +, detectable; −, not detectable.

Discussion

The main focus of cerebral infarction studies has been the neuropathologic changes in the areas directly exposed to ischemia. Consequently, there are few detailed clinical studies on such changes in remote, non-ischemic areas following focal cerebral infarction other than Wallerian degeneration in the cerebral peduncle.8-9 Recently, neuronal degeneration remote from the primary lesion has been studied in laboratory animals. In rats, neuronal loss and atrophy were observed in the ipsilateral thalamus5-5 and the ipsilateral substantia nigra1 a few weeks after MCA occlusion. Since these areas lie outside the ischemic region, degeneration of these areas after MCA occlusion might represent secondary ischemic neuronal damage that takes longer to develop. These neuropathologic changes can be interpreted as the result of either retrograde or anterograde degeneration or transneuronal cell death. In our studies using the MCA occlusion model in rats, we reported coupled increases in local cerebral blood flow and local cerebral glucose utilization and, subsequently, a long-lasting decrease in the concentration of GABA, an inhibitory neurotransmitter, in the ipsilateral substantia nigra pars reticulata.10-11 Our studies, therefore, suggest that the mechanism of neuronal degeneration in the ipsilateral substantia nigra may be a transsynaptic, neurotransmitter-mediated disinhibition as a result of destruction of the striatum.10-11

Are these remote changes observed in humans? Atrophy of the ipsilateral thalamus after cerebral infarction in the territory of the MCA has been revealed by a sequential computed tomographic study.2 Regarding the substantia nigra, there are only a few autopsy reports of neuropathologic changes in this area following massive basal ganglia infarction.6-7 Forno6 reported a slight to moderate nerve cell loss in the ipsilateral substantia nigra, predominantly in the pars compacta, from 6 months to 10 years after massive infarction of the basal ganglia. She interpreted the nerve cell loss in her 10 cases to be a mainly retrograde degeneration, the perineuronal sprout in one case to be a reaction to partial deafferentation, and the paired helical filaments to be either a retrograde or a transsynaptic reaction in the substantia nigra ipsilateral to the basal ganglia destruction. Ohara et al7 reported a marked neuronal loss with gliosis in the ipsilateral substantia nigra in both the pars compacta and the pars reticulata.

In this study, we tried to detect changes in the ipsilateral substantia nigra after striatal infarction using MRI and tried to determine when and where these changes occur. Consequently, we demonstrated a high-signal-intensity spot on T2-weighted images in the ipsilateral substantia nigra, more prominent in the pars compacta, a few weeks after the onset of stroke in the striatal infarction group. This change became obscure a few months later because of decreased signal intensity.
FIGURE 1. Transverse magnetic resonance imaging scans (T2-weighted multiecho images; repetition time 2,000 msec; echo time 100 msec) of case 15 at level of striatum (left) and midbrain (right) 3 days after stroke onset. Infarct is observed in left striatum (arrowheads). No change is seen in midbrain.

FIGURE 2. Transverse T2-weighted magnetic resonance imaging scans of case 15 at level of midbrain 6 (left) and 11 (right) days after stroke onset. Marked high-signal-intensity spot (arrow) is seen in left midbrain 11 days after onset, although tiny high-signal-intensity spot is barely observed in same area at day 6. Lesion is located in substantia nigra.
FIGURE 3. Coronal T2-weighted magnetic resonance imaging scans of case 15 at 11 (left) and 79 (right) days after stroke onset. High-signal-intensity spot is seen in left substantia nigra pars compacta at day 11 (white arrow). This change in ipsilateral substantia nigra became less intense and smaller at day 79. Arrowheads show striatal infarct with perifocal edema.

of the lesion and/or Wallerian degeneration and atrophy in the adjacent cerebral peduncle. No change was observed in the cortical infarction group. It is well known that the substantia nigra is closely related to the corpus striatum. Therefore, striatal infarction must play the same important role in degeneration of the ipsilateral substantia nigra in patients as in MCA-occluded rats. This change in MRI scans may be explained by several mechanisms. Edema, infarction, a focus of gliosis, or a plaque of demyelination may prolong the T2 relaxation time.12 The lesion in our cases was limited to the ipsilateral substantia nigra and was not observed in adjacent structures. Therefore, the lesion was considered less likely to be a vascular lesion than to be a change in the above-mentioned neuronal network.

The neuropathologic change in the substantia nigra was mainly localized in the pars compacta in humans and the pars reticulata in rats. The cause of this

FIGURE 4. Coronal T2-weighted magnetic resonance imaging scans of case 5 at 4 (left), 15 (middle), and 29 (right) days after stroke onset. No change is seen in midbrain at day 4. Fifteen days after onset, small high-signal-intensity spot is observed in ipsilateral substantia nigra. This change became more obvious 29 days after onset (white arrow). At this time, Wallerian degeneration of ipsilateral pyramidal tract is recognized as a low-signal-intensity band (black arrows).
disparity is not apparent, but it may be explained by differences in age, species, or size and distribution of the striatal lesion. As Forno emphasized, many of the animal studies were undertaken on young animals and therefore the age difference may have contributed. The species difference is also important. In rodents, the caudate-putamen forms a large striated mass penetrated by dispersed fiber bundles. The substantia nigra is rudimentary in lower vertebrates, makes a definite appearance in mammals, and reaches its greatest development in humans. Finally, the size and distribution of the striatal lesion is important. The corpus striatum consists of two parts, the neostriatum and the paleostriatum. The former includes the caudate nucleus and putamen. These two components represent a single anatomic and functional entity. The latter comprises the globus pallidus. The striatonigral pathway is mainly a GABAergic inhibitory one, and the pathway from the caudate head and the putamen projects into the pars reticulata while the pathway from the globus pallidus projects into the pars compacta. Mettler reported that a degeneration in the ipsilateral substantia nigra pars reticulata was observed after destruction of the caudate head and putamen, and a degeneration of both the pars compacta and the pars reticulata was observed after destruction of the globus pallidus in primates. On the other hand, the nigrostriatal pathway is a dopaminergic one leading from the substantia nigra pars compacta to the striatum. These fibers traverse the internal capsule and portions of the globus pallidus en route to the putamen. Destruction of the nigrostriatal pathway may also bring about the retrograde degeneration of nigral neurons. Rosegay reported that massive lesions of the head of the caudate nucleus and the anterior limb of the internal capsule gave rise to retrograde degeneration of the pars reticulata and pars compacta of the substantia nigra. Therefore, involvement of the globus pallidus and/or nigrostriatal pathway may play an important role in degeneration of the ipsilateral substantia nigra pars compacta. Further detailed study is required to confirm this hypothesis.

Neuronal death in a remote area following focal infarction is a very interesting phenomenon. It is possible that the chronic pathophysiology of infarction, especially parkinsonism and vascular dementia, may be clarified by the study of these changes. MRI is very useful in following neuropathologic changes after cerebral infarction and will yield much information on cerebral ischemia.

References
Degeneration of the ipsilateral substantia nigra following cerebral infarction in the striatum.
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