Thalamic Atrophy Following Cerebral Infarction in the Territory of the Middle Cerebral Artery

Akira Tamura, MD, DMS; Yoshihiro Tahira, MD; Hiroshi Nagashima, MD; Takaaki Kirino, MD, DMS; Osamu Gotoh, MD, DMS; Shuntaro Hojo, MD, DMS; and Keiji Sano, MD, DMS

We investigated shrinkage of the ipsilateral thalamus following infarction in the territory of the middle cerebral artery in 33 patients who were admitted ≤2 days after the stroke and who were followed by computed tomography for >1 year with no recurrences. The thalamic area was measured on the computed tomograms, and the ratio of the ipsilateral area to the contralateral area was calculated. All values were compared with values from the initial computed tomogram taken ≤2 days after the stroke. The values of the ratio on follow-up computed tomograms decreased gradually in 15 patients. In these cases, the area of the ipsilateral thalamus was significantly reduced after 1 year (p<0.01) and marked atrophy was observed. These results demonstrate the significance of remote changes over a long period of time after focal cerebral infarction. (Stroke 1991;22:615–618)

It has been widely believed that neuronal alterations following cerebral ischemia progress rapidly. Therefore, the main issue of neuropathologic studies after cerebral ischemia has been acute neuronal changes in the ischemic area. In 1982, Kirino found a strikingly slow process of neuronal change in the hippocampal CA1 subfield following brief cerebral ischemia, which he called “delayed neuronal death.” Since then, delayed neuropathologic changes following cerebral ischemia have attracted widespread attention. These changes are also found in the area exposed to ischemia.

The aim of this study was to analyze neuropathologic changes in a distant, nonischemic area after focal cerebral ischemia. We particularly focused on delayed neuropathologic changes of the ipsilateral thalamus following infarction in the territory of the middle cerebral artery (MCA).

Subjects and Methods

A total of 109 patients with cerebral infarction were admitted to our clinic from 1985 through 1989.

From among these patients, we selected 33 who 1) were admitted ≤2 days after the first attack of stroke, 2) had a single low-density area on an initial or follow-up computed tomogram (CT film) in the MCA territory, 3) were followed by symmetrical CT at the level of the thalamus for >1 year, and 4) developed no symptomatic or asymptomatic recurrence of stroke on CT. In these patients, the area of the thalamus on each side was randomly measured with a computerized digitizer on the CT films at the level of the thalamus according to a CT atlas 1, 3, and 6 months and 1 and 2 years after the stroke. The CT films were taken in parallel planes at an angle of 15° to the infraorbital line. The area surrounded by the posterior limb of the internal capsule and the third ventricle was measured as the area of the thalamus (Figure 1). The ratio of the ipsilateral area to the contralateral area of the thalamus was calculated.

Values of the ratio on follow-up CT films were compared with values obtained from the initial CT film taken ≤2 days after the stroke. The mean and standard deviation (SD) of the ratio in the initial CT film were calculated. The range of 2 SDs indicates the 95% confidence interval. Therefore, values outside this range were regarded as abnormal.

Results

The mean and SD of the ratio in the initial CT films were 0.990 and 0.064, respectively. Thus, the 95% confidence interval was 1.118–0.862. In 15
patients, the ratio in the follow-up CT films was outside this range (atrophic group). Figure 2 shows the time courses of the values in these 15 patients. The ipsilateral thalamus gradually decreased in size from 3 months after the stroke, and marked atrophy was observed after 1 year (Figure 3). The mean±SD contralateral thalamic area was 331.4±47.5 mm² on the initial CT films and 313±57.7 mm² at 1 year after onset in the atrophic group and 309±46.0 mm² initially and 304±49.5 mm² at 1 year in the nonatrophic group. On the other hand, the ipsilateral area was 320.7±44.8 mm² initially and 223.5±37.7 mm² at 1 year in the atrophic group and 308.6±48.0 mm² initially and 297.3±46.3 mm² at 1 year in the nonatrophic group. The area of the ipsilateral thalamus 1 year after stroke onset was significantly less than the initial value in the atrophic group (<0.01 by Student’s paired t test).

Figure 2. Time course of ratio of ipsilateral to contralateral thalamic area of 15 patients in atrophic group. Hatched area represents range of 2 standard deviations (SDs) on initial computed tomograms taken ≤2 days after stroke.

Figure 3. Computed tomograms of case 5 in Figure 4 at 1 day (1D), 3 months (3M), 6 months (6M), and 1 year (1Y) after onset of stroke. Marked atrophy of ipsilateral thalamus is observed 1 year after onset.
Figure 4 shows the area of infarction in each patient in the atrophic group and the typical patterns in the nonatrophic group. In the atrophic group, side of infarction and number of patients are shown. R, right; L, left.

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<tr>
<th>Atrophic Group</th>
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<td>Case 1</td>
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Discussion

In 1981, we developed a focal cerebral ischemia model in rats by occluding the stem of the MCA. Neuropathologic study showed ischemic brain damage in the cortex and basal ganglia, but not in the thalamus. Recently, we reported a neuropathologic study of the ipsilateral thalamus following MCA occlusion in rats. In that study, neuronal necrosis in the ipsilateral thalamus was seen 2 weeks after MCA occlusion. Later, the entire half of the thalamus progressively shrank during the several months following occlusion. Since the thalamus lies outside the ischemic area, shrinkage of the ipsilateral thalamus after MCA occlusion might be a secondary ischemic neuronal damage that takes longer to develop. Most important is the fact that neuropathologic change is never seen in this remote area during the acute phase of focal cerebral ischemia. Our study shows that atrophic changes in the ipsilateral thalamus similar to those found in the rat MCA occlusion model also occur in patients with cerebral infarction in the MCA territory.

There are two possible explanations for shrinkage of the thalamus in patients: primary change due to coexistent thalamic ischemia or subsequent asymptomatic infarction in the thalamus and secondary degeneration through neural connections with the primary infarcted area. The former explanation is unlikely for two reasons. First, the vascular supplies of the thalamus and MCA territory are different. The thalamus is nourished mainly by branches of the posterior cerebral artery, which frequently obtains its greatest source of blood through the basilar artery. Second, such low-density areas in the thalamus did not appear on the CT films, which were usually taken on the day of admission and 1 and 2 weeks and 1 and 3 months after the stroke and then every 3 months. Thus, thalamic atrophy is more likely to be a secondary lesion.

We propose two types of neuronal degeneration (anterograde and retrograde) as the cause of secondary degeneration in a remote area following focal damage. After sectioning, an axon undergoes Wallerian degeneration. The axon degenerates, as do its terminals and its surrounding myelin sheath. These changes are referred to as anterograde degeneration. Conversely, severing an axon also causes the cell body of the affected neurons to react. This is retrograde degeneration. In addition, both types of degeneration may have an effect across a synapse: transneuronal anterograde and retrograde changes.

In our CT study, we cannot explain the cause of secondary thalamic degeneration. However, judging from several other experimental studies, thalamic atrophy may primarily result from retrograde degeneration. In the MCA occlusion model in rats, Kataoka et al studied disturbances of the neuronal network after focal ischemia using Fink-Heimer silver impregnation and succinate dehydrogenase histochemistry. In that study, massive silver staining of degenerated synaptic terminals and decreases in succinate dehydrogenase activity were observed in the ipsilateral thalamus 4 and 5 days after occlusion. These authors considered that the absence of succinate dehydrogenase staining reflects early changes in retrograde degeneration of thalamic neurons after ischemic injury of the thalamocortical pathway. Izuka et al also reported a similar result using the same model and concluded that their findings were consistent with retrograde neuronal degeneration. A similar degeneration of thalamic neurons has been well-documented after cortical ablation, a classical technique for showing neuronal links in the central nervous system. Since 1870, when Gudden
provided evidence of an intimate link between the thalamus and cerebral cortex by showing that ablation of the cortex led to the death and disappearance of cell bodies in the thalamus, several studies have shown neuronal death and later atrophy in the ipsilateral thalamus following cortical ablation. Using electron microscopy, Matthews reported thalamic retrograde degeneration following cortical ablation in rabbits. In that study, unequivocal signs of retrograde alteration became evident within the affected thalamic nuclei by the second postoperative day, progressing to the disappearance of many perikaryal profiles within the first 7–10 days. Most thalamic neurons examined in that investigation disappeared within 2 weeks after cortical ablation and, from the fourth to the 34th postoperative week, all remaining neurons gradually disappeared from the zones of degeneration. Therefore, Matthews concluded that thalamic degeneration resulted mainly from retrograde degeneration in axotomized thalamic neurons, although thalamic degeneration was also partially due to anterograde degeneration of corticofugal axons. These experimental results coincide quite well with our clinical observations, suggesting that thalamic atrophy following cerebral infarction in the MCA territory is due to retrograde degeneration.

There are few detailed studies on neuropathologic changes in remote, nonischemic areas following focal cerebral infarction other than Wallerian degeneration and atrophy in the cerebral peduncle. In our present study, we report delayed neuropathologic change in the thalamus, a distant, nonischemic area, after focal cerebral infarction in the MCA territory. It has been well recognized that thalamic damage is associated with aphasis disturbances (thalamic aphasia) and amnestic syndromes (thalamic dementia). In our study, one third of the patients in the atrophic group showed sustained dementia. However, it is very difficult to analyze the cause of dementia from our preliminary study because of the small number of patients. Further study is required to confirm the clinical meaning of thalamic atrophy. Our results do demonstrate the significance of remote changes over a long period of time following focal brain injury, a phenomenon that could be important in understanding the pathophysiologic changes during the chronic phase of cerebral infarction.

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