Secondary Neurodegeneration in Remote Regions After Focal Cerebral Infarction

A New Target for Stroke Management?

Jian Zhang, MD, PhD; Yusheng Zhang, MD, PhD; Shihui Xing, MD, PhD; Zhijian Liang, MD, PhD; Jinseng Zeng, MD, PhD

Cerebral infarction-induced cessation of function in areas of the brain remote from, but connected to, the primary site of damage was termed “diaschisis” by von Monakow. Initially, the concept of diaschisis did not include morphological changes. However, accumulating evidence has shown that histopathologic changes also occur in nonischemic remote brain regions that have synaptic connections with the primary lesion site. For example, after cerebral infarction in the middle cerebral artery (MCA) territory, neuronal death, gliosis, and axonal degeneration have been found in the ipsilateral thalamus, substantia nigra (SN), and distal pyramidal tract, all of which lie outside the MCA territory. This kind of secondary neurodegeneration occurs selectively in such areas several days or weeks after stroke onset, and this can be detected by neuroimaging techniques. For quite a long time, the role of secondary degeneration in stroke recovery has not been well understood. Recently, emerging studies suggest that secondary degeneration is associated with neurological deficits and can predict motor outcome after stroke.

In this review, we aimed to summarize the pathological and neuroimaging evidence of secondary neurodegeneration in the ipsilateral thalamus, SN, and pyramidal tract after MCA infarction and described its potential significance for stroke management. We searched PubMed from 1980 to September 2011, using the terms “cerebral infarction,” “middle cerebral artery,” “Wallerian degeneration,” “anterograde degeneration,” “retrograde degeneration,” and “transneuronal degeneration.” Further articles were identified from the references cited in those articles and through searches of our personal files. The final list of references was selected on the basis of originality and relevance to the topics covered in this review.

Evidence of Secondary Degeneration After Stroke

Postmortem Studies
Data from postmortem studies provide direct evidence of secondary neurodegeneration after focal cerebral infarction (Figure 1). Histopathologic examination at 4 months after MCA infarction revealed a delayed and selective decrease in the neuron density, neuropil rarefaction, and reactive astrocytosis in the ipsilateral thalamus. Different from the pathological features of primary infarction, macrophages were rare in the thalamus. This secondary lesion cannot be explained by insufficient blood supply, and it may reflect retrograde degeneration of the thalamocortical fibers.

The SN is another brain structure that is subjected to secondary degeneration after MCA infarction. Forno reported 10 cases of slight to moderate nerve cell loss in the compact zone of the ipsilateral SN ranging from 6 months to 10 years after massive unilateral infarction of the basal ganglia. One case displayed perineuronal sprouts and paired helical filaments in the ipsilateral SN. The neuronal loss was interpreted as being mainly retrograde degeneration of the nigrostrial fibers, the perineuronal sprouts as a reaction to partial deafferentation, and the paired helical filaments as either a retrograde or a trans-synaptic reaction.

Additionally, MCA infarction also causes Wallerian degeneration of the distal pyramidal tract. Buss et al investigated temporal changes in the Wallerian degeneration in the spinal cords of patients who died 2 days to 30 years after either cerebral infarction or traumatic spinal cord injury, and they found axonal loss, myelolysis, and astrocytic reactions. The appearance of these pathological changes is delayed relative to the infarction, starting from the segments close to the lesion site and extending to the distal segments. For example, axonal loss and myelolysis first appeared in the corticospinal tract of the cervical segment 2 weeks after stroke onset and then progressed to the lumbar segment at 5 weeks. Similarly, no astrocytic reaction was detected in the degenerating corticospinal tract until 4 months after injury. Moreover, activated microglia were found in the descending corticospinal tract at a delayed stage after cerebral infarction. Human leukocyte antigen -DA–positive microglia were detected in the gray matter of the spinal cord contralateral to the infarct within 2 weeks after stroke. As survival time...
progressed from 5 weeks to 4 months, the numbers of human leukocyte antigen-DA–positive microglia decreased in the gray matter but were abundant within the contralateral corticospinal tract. Although the role of these activated microglia in Wallerian degeneration was unclear, they were believed to contribute to removal of the degenerating axons.6,7

**Plain CT and Conventional MRI**

The neuroimaging features of secondary neurodegeneration have been summarized in the Table. The CT scan revealed atrophy of the thalamus and pyramidal tract at the chronic phase after massive cerebral infarction. Tamura et al16 first reported progressive shrinkage of the ipsilateral thalamus after MCA infarction in 15 (45.5%) of the 33 patients. In the study, the thalamic area gradually decreased starting at 3 months after stroke onset and disappeared thereafter.23,24 More importantly, recent studies reported that diffusion-weighted imaging hyperintensity or apparent diffusion coefficient map hypointensity in the pyramidal tract was correlated with poor motor outcome, suggesting that a diffusion-weighted imaging signal abnormality in the pyramidal tract is an early predictor of motor recovery after cerebral infarction.9–11

In 2 longitudinal diffusion tensor imaging studies, a significant increase in mean diffusivity was noted in the ipsilateral thalamus 1 to 6 months after MCA infarction, whereas fractional anisotropy (FA) remained unchanged.25,26 The increased mean diffusivity is probably attributable to a progressive loss of cell membranes—the most important barriers of water movement—and the lack of FA changes may be related to the absence of isolated bundles of parallel fibers within the thalamus.25 Consistently, our study using diffusion tensor imaging and proton magnetic resonance spectroscopy revealed a decrease in location of the basis pedunculi shrinkage was determined by the primary infarction site. These results suggest that secondary degeneration can be predicted by the location and extent of the primary ischemic lesions.

In contrast with CT, MRI is more sensitive to secondary degeneration after stroke. A hyperintense area was detected on T2-weighted spin-echo images within the ipsilateral thalamus in 14 (47%) of the 30 patients with embolic cerebral infarction.2 Interestingly, signal abnormality on T2-weighted images varied in different nucleus of the thalamus. A hyperintense signal was detected within the dorsiomedial and pulvinar nucleus at 6 weeks after cerebral infarction, whereas a hypointense signal was revealed within the ventral nuclei a few weeks after infarction.18 Besides the thalamus, MRI also can reveal the secondary degeneration in the SN. In patients with striatal infarction, T2-weighted images revealed a hyperintense spot in the ipsilateral SN. This abnormal spot appeared after an average of 14.3 days after the stroke onset and then became less intense 3 months after onset.19

Wallerian degeneration of the pyramidal tract displays an evolution of signal changes on T2-weighted and proton density-weighted images. Within 1 month, no abnormalities were found in the ipsilateral basis pedunculi or basis pontis. At 1 to 3 months, a hypointense band was evident in these areas. The low signal then evolved to be hyperintense and stabilized at 3 months after stroke onset. Over the course of 6 to 12 months, shrinkage of the ipsilateral basis pedunculi and basis pontis occurred.20,21 The temporal low signal on T2-weighted and/or proton density-weighted images may result from a transiently increased lipid–protein ratio because of myelin sheath degradation, whereas the high intensity reflected increased water content in the enlarged extracellular spaces.20

**Diffusion-Weighted Imaging and Diffusion Tensor Imaging**

In a case report study, a transitory diffusion-weighted imaging hyperintense lesion accompanied by a decreased apparent diffusion coefficient value was noted in the ipsilateral SN within 2 weeks after MCA infarction.22 Additionally, a similar evolution of signal change also was detected in the area of pyramidal tract: a high signal on diffusion-weighted imaging and low apparent diffusion coefficient value were evident in the first 2 weeks after stroke onset and disappeared thereafter.23,24 More importantly, the temporal low signal on T2-weighted and/or proton density-weighted images may result from a transiently increased lipid–protein ratio because of myelin sheath degradation, whereas the high intensity reflected increased water content in the enlarged extracellular spaces.20

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N-acetylaspartate concentration, a marker for neuronal and axonal integrity and function, in the ipsilateral thalamus after subcortical infarction. Different from the thalamus, the pyramidal tract is composed of parallel fibers. Therefore, a marked reduction in FA values was found in the descending pyramidal tract distal to the primary infarction, accompanied by increased or unaltered mean diffusivity. Interestingly, decreased anisotropy was associated with motor outcome after stroke. Our prospective cohort studies further investigated the association between FA changes in the pyramidal tract above and below the primary infarcts and neurological deficits (Figure 2). The results demonstrated that FA values decreased progressively over 1 to 12 weeks in the pyramidal tract, both proximally and distally to a subcortical cerebral infarct or pontine infarct. Moreover, the percent reductions in FA value were negatively correlated with the percent changes in National Institutes of Health Stroke Scale and the Fugl-Meyer scale.

**Potential Therapeutic Targets**

Because secondary degeneration occurs several days or weeks after stroke onset and the therapeutic time window for such lesions is not as narrow as that of the primary infarction, it is expected that the development of therapies targeting secondary degeneration would enhance brain plasticity and improve functional outcomes. In fact, secondary degeneration after MCA occlusion has been shown in experimental studies (Figure 3), and several potential therapeutic targets have been proposed.

**Apoptosis**

Morphological features indicative of apoptosis, such as DNA fragmentation, nuclear condensation, and apoptotic bodies, have been observed in the ipsilateral thalamus after focal cerebral infarction in rats. Terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling is a marker of double-strand DNA damage. After MCA occlusion, terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling–positive cells were evident in the ipsilateral ventrobasal thalamus. Interestingly, the terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling–positive cells in the thalamus displayed concurrent apoptotic and necrotic alterations under electron microscopy. Moreover, caspase-3 activity was markedly increased in the terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling–positive cells. Treatment with a caspase inhibitor significantly reduced the number of terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling–positive cells in the ipsilateral thalamus. These findings suggest that apoptosis may be involved in the secondary thalamic degeneration. In addition, the observation that antiapoptotic Bcl-2 expression was reduced in the thalamus following MCA occlusion has been shown in experimental studies (Figure 3), and several potential therapeutic targets have been proposed.

**Table. Neuroimaging Features of Secondary Neurodegeneration After Middle Cerebral Artery Infarction**

<table>
<thead>
<tr>
<th>Thalamus</th>
<th>Substantia Nigra</th>
<th>Pyramidal Tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain CT</td>
<td>Gradually decreased in size starting at 3 mo after stroke</td>
<td>Not reported</td>
</tr>
<tr>
<td>MRI T2 and/or PDWI</td>
<td>Hypointensity in the ventral nuclei a few weeks after stroke</td>
<td>Hyperintensity on T2WI at 1 or 2 wk after stroke and becomes less intense 3 mo later</td>
</tr>
<tr>
<td>MRI DWI</td>
<td>Not reported</td>
<td>Transient hyperintensity on DWI with decreased ADC within 2 wk after stroke</td>
</tr>
<tr>
<td>DTI</td>
<td>Increased MD values at 3 mo after stroke onset, with FA values unchanged</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

ADC indicates apparent diffusion coefficient; CT, computed tomography; DTI, diffusion-tensor imaging; DWI, diffusion-weighted imaging; FA, fractional anisotropy; MCA, middle cerebral artery; MD, mean diffusivity; MRI, magnetic resonance imaging; PDWI, proton density-weighted imaging; T2WI, T2-weighted imaging.

**Figure 2.** Secondary degeneration in the pyramidal tract and middle cerebellar peduncle after pontine infarction. A and B, Fluid-attenuated inversion recovery (FLAIR) image and diffusion tensor tracography (DTT), respectively. The white arrow indicates the pontine infarction site. The purple arrow indicates the degeneration of pyramidal tract superior and inferior to the infarction. The blue arrow indicates the degeneration of the ipsilateral middle cerebellar peduncle.
amus and that Bcl-2 overexpression in transgenic mice prevented the neuronal loss in the thalamus further supports the possible involvement of apoptosis in secondary degeneration after cerebral infarction.32,33

**Inflammatory Reaction**

In humans and animals, cytokine upregulation and microglial/astrocytic reactions have been frequently detected before or concurrently with neuronal damage at remote regions after focal cerebral infarction. A recent review of inflammation in a remote area after focal brain lesion has discussed this aspect in detail.8 The inflammatory response seems to be an early event in secondary neurodegeneration. In the ipsilateral thalamus, tumor necrosis factor-α was upregulated 1 day after MCA occlusion, and the microglial/astrocytic reaction was activated after 3 days.34 In contrast, neuronal degeneration was initiated only 4 days after MCA occlusion, and it became evident after 14 days.34,35 Some evidence supports the idea that the inflammatory response may contribute to neuronal damage. Osteopontin, a secretory product of activated macrophages, was reported to be protective against secondary thalamic lesions via antiinflammatory effects.36 Additionally, astrocytic scarring in the spinal cord after cerebral infarction was believed to form an environment that is unfavorable for axonal regeneration.4 Nevertheless, the role of the inflammatory reaction in the neuronal damage at remote regions has not been fully elucidated. It remains unclear whether the inflammatory response is merely a consequence of brain lesions.

**Neurotoxic and Neuroinhibitory Factors**

Neurotoxic and neuroinhibitory factors also may be involved in secondary lesions after focal cerebral infarction. Retrograde and anterograde degeneration of fibers may cause excitotoxicity in remote regions, leading to neuronal death. For example, the pars reticulata of the SN receives GABAergic inhibitory projections from the striatum and glutamatergic inputs from the subthalamic nucleus.8 Striatal infarction may impair inhibitory afferents to the reticulata of the SN, leading to increased metabolism and neuronal death.35 Consistent with this presumption, treatment with MK-801 (glutamate N-methyl-d-aspartate receptor antagonist) as well as YM872 (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor antagonist) can reduce secondary degeneration in the reticulata of the SN after MCA occlusion.37,38

Figure 3. Amyloid-beta (Aβ) deposits, neuronal loss, and glial activation in the ipsilateral thalamus at 14 days after middle cerebral artery occlusion in rats. A, Aβ immunostaining (star and arrow indicate infarct and Aβ deposits, respectively). NeuN (neuronal marker; B), GFAP (astrocytic marker; C), and OX42 (microglial marker; D) immunostaining, respectively. Scale bars in (A, B) apply to (A–D), respectively.
Amyloid-beta (Aβ), a main constituent of senile plaque in Alzheimer disease, is known to be neurotoxic. In the ipsilateral thalamus, Aβ accumulated abnormally and aggregated to plaque-like deposits for up to 9 months after MCA occlusion. We investigated the association of Aβ with secondary thalamic damage and found that administration of a functional γ-secretase inhibitor significantly reduced Aβ deposits and neuronal loss in the thalamus, suggesting that Aβ deposits may be associated with secondary thalamic damage.

In addition to Aβ, Nogo-A, which can inhibit axonal growth, also has been shown to be upregulated within 4 weeks after MCA occlusion. The elevation of Nogo-A may contribute to maintaining an environment that is hostile to axonal regeneration. Treatment with a Nogo-66 receptor antagonist NEP1–40 can block the effect of Nogo-A and lead to enhanced axonal regeneration and attenuation of neuronal degeneration.

Oxidative Damage
Oxidative damage to nDNA not only contributes to neuronal damage in the primary infarction but also participates in the pathogenesis of secondary neurodegeneration in remote regions. After focal cerebral infarction, endogenous antioxidant defenses were activated at the remote regions. Increased immunoreactivity of manganese–superoxide dismutase and expression of damage-induced neuronal endopeptidase mRNA was observed in the ipsilateral thalamus after MCA occlusion in rats. Superoxide dismutases are known to effectively scavenge superoxide radicals and protect neurons from oxidative damage, and damage-induced neuronal endopeptidase can be upregulated in response to neuronal insult and activate superoxide dismutases. Therefore, the elevation of manganese–superoxide dismutase and damage-induced neuronal endopeptidase may reflect increased oxidative stress in the ipsilateral thalamus.

Our study in rats revealed enhanced expression of 8-hydroxy-2′-deoxyguanosine and decreased expression of 8-oxoguanine DNA glycosylase in the ipsilateral thalamus after MCA occlusion, indicating an imbalance between oxidative DNA damage and the base repair activity ratio. Furthermore, treatment with ebselen, an antioxidant, significantly attenuated the increased 8-hydroxy-2′-deoxyguanosine expression, ameliorated the decreased 8-oxoguanine DNA glycosylase expression, and reduced the neuronal loss in the ipsilateral thalamus.

Macroautophagy
Macroautophagy is a lysosomal pathway for the recycling of intracellular organelles and proteins and plays multiple roles in cell homeostasis. It has been suggested that macroautophagy can promote cell survival in chronic brain diseases and can mediate cell death in acute neurological disorders, implicating the effects of macroautophagy are context-dependent. We investigated the role of macroautophagy in the secondary thalamic degeneration after cerebral cortical infarction in rats and found that macroautophagy was activated in the ipsilateral thalamic cells. Furthermore, macroautophagic inhibitor and Beclin-1 knockdown significantly reduced the macroautophagic activation and neuronal loss, suggesting macroautophagy may act in cell death in secondary thalamic degeneration. To further understand the role of macroautophagy in secondary degeneration, it is necessary to investigate exactly how macroautophagy contributes to cell death and its relationship with other cell death pathways. Interestingly, there is cross-talk between macroautophagy and Aβ deposits. Inhibition of macroautophagy prevented the Aβ accumulation and, conversely, reduction of Aβ suppressed macroautophagy activation. Further studies are needed to elucidate the underlying mechanisms.

Future Perspectives
The findings that neuroprotective agents can reduce the secondary degeneration and associate with functional improvement in animal stroke models are appealing. However, the question we constantly face is whether these effects can be translated into the clinic. Several issues should be considered before entering into clinical trials. First, most of the experimental studies targeting secondary degeneration merely assess the histological outcomes in the remote regions. More experimental studies are needed to evaluate the functional outcomes, which are the primary measures of therapeutic efficacy in clinical trials. Second, the mechanisms involved in the development of secondary degeneration have not been fully elucidated. A better understanding of the underlying mechanisms may help to identify the appropriate therapeutic targets in clinical trials. Third, our recent study has showed there are neurogenesis and angiogenesis within the ipsilateral thalamus after focal cerebral infarction, suggesting the regeneration is coupled with the damage. It also would be interesting and important to investigate the role of neurogenesis and angiogenesis in stroke recovery.

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Disclosures
None.

References


**Key Words:** cerebral infarction, secondary neurodegeneration, computed tomography, magnetic resonance imaging, thalamus, pyramidal tract
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Figure 1. Secondary neurodegeneration after middle cerebral artery (MCA) infarction. Focal cerebral infarction in the MCA territory not only causes neuronal damage in the area of ischemia but also affects nonischemic regions that have synaptc connections with the primary lesion site, such as the ipsilateral thalamus, the substantia nigra (SN), and the distal pyramidal tract. Pathological changes include neuronal death, axonal deafferentation, and gliosis. MCAdt, middle cerebral artery deep territory; MCAst, middle cerebral artery superficial territory; Puta, putamen; Thal, thalamus.

ineuronal sprouts와 이중나선성유가 관찰되었다. 신경손실은 흑질 신경섬유다발의 후행적 변성으로, 신경주위 병변은 부
먼적인 구조로 치환(deafferentation)으로, 이중나선성유는 후행적
또한 시냅스 통과성 반응(trans-synaptic reaction)으로 설명하였다.3

추가로, 증대뇌동맥영역의 뇌경색은 원위부 추체로의 왼
변성을 일으킨다. Buss 등은 뇌경색 또는 외상성 화학손상이
발생한 이후 2일에서 30일 사이에 사망한 환자들의 착수에서
와병변의 시간적 변화를 연구하였으며,4 축삭의 소실, 수초
용해증, 성상세포 반응을 확인하였다. 이러한 뇌실질적 변화
뇌경색에 비해 지연되었으며, 병변과 가까운 부위에서
시작하여 반으로 퍼졌다. 예를 들어, 뇌증후 뇌경색 2주 후에
경추부의 피질척수로에 축삭 소실과 수초용해증이 처음 발
현되며, 이후 5주째에 최우부위까지 진행한다.5 비슷하게, 손
상 이후 4개월까지는 변성된 피질척수로 내에서 성상세포생
반응은 관찰되지 않았다.6,7 또한, 활성화된 미세아교세포도 뇌
경색 발생 후 시간이 지난 후에 하행 피질척수로에서 관찰되
었다. 사람백혈구항원(Human leukocyte antigen)–DA 양
성인 미세아교세포가 뇌증후 발생 이후 2주 이내에 뇌경색과
반대측 척수의 회색질에서 발견되었다.6,7 5주부터 4개월까지
생존시간이 진행함수록 반대측 피질척수로에서 회색질의 사람
백혈구항원–DA 양성 미세아교세포는 감소하지만, 그래도 꾸
부하게 관찰되었다. 활성변성에서 이 활성화된 미세아교세포
의 역할은 불분명하지만, 변성된 축성의 제거에 역할을 담당하
라 생각된다.6,7

단순 CT와 일반 MRI
이차 신경변성의 신경영상학적 형태를 Table에 정리했다. 큰
뇌경색 발생 이후 반응기에 시상고 추체로의 위치를 CT로
확인할 수 있다. Tamura 등은 중대뇌동맥 영역 뇌경색 환자
33명 중 15명(45.5%)에서 동측의 시상가 점차 위치까지 감소
한 것으로 보고하였다.8 이 연구에서 뇌증후 발생 3개월 이후부
터 시상 후반각 좌측 감소하기 시작해서, 1년 이후에 확연한 위
축을 보였다.9 주목할만한 점은 위치성 변화가 뇌경색의 크기,
위치와 연관되어 있어 보인다는 점이다. Warabi 등은 기저각
(basis pedunculi)의 위치와 일차손상영역과의 연관성을 89
명의 만성 신경세포마라 환자에서 연구했으며, 기저각이 위치는
부분이 일차뇌경색 위치에 의해 결정된다는 것을 발견하였다.10 이
결과로 2차 변성은 일차 헬레손상 영역의 위치와 범위에
의해 예측될 수 있다는 것을 알 수 있다.

CT와 MRI는 뇌증후 이후 이차변성에 좀 더 민감하
다. 사전성 뇌경색 환자 30명 중 14명(47%)에서 동측의 시상
내에 고강도음영 영역이 T2장조 소견으로 영상에서 관찰되었
다.10 흉미령계도, 시상의 각 핵들에서 T2장조영상에서의 신호
이상 정도가 다양했다. 뇌경색 이후 6주째에 동측대뇌척과 시
상세계기에 고장실신호가 관찰된 반면, 뇌경색 이후 수주
에 부진하게는 저장도증신호가 관찰되었다.11 시상 외에, 흉미
역에서도 MRI에서 이차변성을 확인할 수 있다. 선조제 뇌경색
환자에서, 동측의 흉미도 심한 과도로 나타나는 저지선 T2장조
영상에서 확인되었다. 이 비정상 병변은 뇌증후 발생 이후 평
균 14.3일 이후에 나타났으며, 중상발생 3개월 후에는 강도가
약해졌다.12

추체로의 활성변성은 T2장조영상과 양성자 및 양성 영상
에서 신호변화의 진행을 보여준다. 1개월 이내에는 동측의 기
저각이나 뇌교기저부에 아무 이상도 발견되지 않았다. 뇌경색
발생 이후 1~3개월의 시점에, 이들 영역에 저강도 피가 나타
난다. 저강도 신호는 점차 고강도 신호로 바뀌고 이후 3개월에
큼 약화된다. 6~12개월의 시점에는, 동측의 기저각과 뇌교
기저부의 위치가 이동한다.13,14 T2장조영상과 양성자에 보인
장조 영상에서 일시적으로 저강도 신호가 나타나는 것은 아마도 수
Table. Neuroimaging Features of Secondary Neurodegeneration After Middle Cerebral Artery Infarction

<table>
<thead>
<tr>
<th></th>
<th>Thalamus</th>
<th>Substantia Nigra</th>
<th>Pyramidal Tract</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plain CT</td>
<td>Gradually decreased in size starting at 3 mo after stroke$^{16}$</td>
<td>Not reported</td>
<td>Shrinkage of the basis pedunculi and pontis at 1 y after stroke$^{17}$</td>
</tr>
<tr>
<td>MRI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2 and/or PDWI</td>
<td>Hypointensity in the ventral nuclei a few weeks after stroke$^{18}$</td>
<td>Hyperintensity on T2WI at 1 or 2 wk after stroke and becomes less intense 3 mo later$^{19}$</td>
<td>No abnormal intensity within 1 mo after stroke</td>
</tr>
<tr>
<td></td>
<td>Hyperintensity in the dorsomedial and pulvinar nucleus at 6 wk after stroke$^{20,21}$</td>
<td></td>
<td>Hypointensity 1–3 mo after stroke</td>
</tr>
<tr>
<td>DWI</td>
<td>Not reported</td>
<td>Transient hyperintensity on DWI with decreased ADC within 2 wk after stroke$^{22}$</td>
<td>Transient hyperintensity on DWI with decreased ADC within 2 wk after stroke$^{23,24}$</td>
</tr>
<tr>
<td>DTI</td>
<td>Increased MD values at 3 mo after stroke onset, with FA values unchanged$^{25,26}$</td>
<td>Not reported</td>
<td>Reduced FA values at both acute (1 wk) and chronic stages (several years)$^{25,27}$</td>
</tr>
</tbody>
</table>

$^{16}$ADC indicates apparent diffusion coefficient; CT, computed tomography; DTI, diffusion-tensor imaging; DWI, diffusion-weighted imaging; FA, fractional anisotropy; MCA, middle cerebral artery; MD, mean diffusivity; MRI, magnetic resonance imaging; PDWI, proton density-weighted imaging; T2WI, T2-weighted imaging.

ADC indicates apparent diffusion coefficient; CT, computed tomography; DTI, diffusion-tensor imaging; DWI, diffusion-weighted imaging; FA, fractional anisotropy; MCA, middle cerebral artery; MD, mean diffusivity; MRI, magnetic resonance imaging; PDWI, proton density-weighted imaging; T2WI, T2-weighted imaging.

초의 과료로 인해 일시적으로 지질-단백 비율이 증가하기 때문에 생각되고, 고강도 신호는 세포의 공간이 증가함에 따라 수분 흡수량이 증가하는 것을 반영하는 것으로 보인다.$^{20}$

환산강조영상과 확산텐서영상

중대연구에서, 중대뇌동맥 영역 뇌경색 발생 2주 이내에 일시적으로 확산강조영상에서 고강도 신호를 보이고, 결박이 확산 계수는 감소한 영역이 동측 혹은에서 관찰되었다.$^{22}$ 추가로, 추 체로변역에서 비슷한 신호 변화의 발전이 관찰되었는데, 뇌졸 량 발생 이후 2주까지 확산강조영상에서는 고신호강도를 보이면서 결박이 확산 계수가 감소한 상태가 나타났다고, 이후 사라졌다.$^{23,24}$ 좀 더 중요한 것은, 최근의 연구에서 추체로가 확산강조영상에서 고강도 신호를 보이거나 결박이 확산 계수 지도에서 저강도 신호를 보이는 것이 운동기능의 브렌 예후와 연관되어 있어, 추체로의 확산강조영상 신호이상이 뇌경색 이후 운동기능 회복의 초기 예측인자로 제안되고 있다.$^{25,26}$

두 개의 확산텐서영상 추적 연구에서, 중대뇌동맥 영역 뇌경색 이후 1~6개월 시점에 동측의 시상에서 평균 확산성의 유의한 증가가 관찰되었다. 그 반면 비등방도(fractional anisotropy, FA)는 변화가 없었다.$^{25,26}$ 평균 확산성이 증가한 것은 물질러 운동에서 가장 중요한 제안을 세포의 집합적 소실에 기인하며 FA가 변화하지 않은 것은 아마도 시상 내에 분리된 평행 손서방향이 없기 때문인 것으로 생각된다.$^{23}$ 이와 일관되게, 확산텐서영상과 양성자 자기공명 분광법을 이용한 저자들의 연구에서는, 피질의 뇌경색 이후 동측 시상에서 N-acetylaspartate 농도가 감소되었는데, 이는 신경세포, 세포의 완전성과 기능의 표지자이다.$^{27}$ 사망과의 멀리 추체로는 평행한 손서방향으로 이루어져 있다. 그러하여, 일자 뇌경색의 원 위부의 하행성 추체로에서 FA값의 주목할만한 감소가 나타나며, 평균 확산성은 증가하거나 변화가 없었다.$^{25,26}$ 희미롭게도, 이방성(anisotropy)이 감소하는 것은 뇌졸 량 발생 후 운동기능의 예후와 연관되어 있었다.$^{23}$ 저자들의 전향적 연구에서 일자 뇌경색의 위, 아래의 추체로의 FA 변화와 신경학적 손상의 연관성을 연구했었다(Figure 2), 그 결과 피질하 뇌경색이나 뇌교차의 뇌경색에서 추체로의 근위부, 원위부 모두 1~12 주에 걸쳐 FA값이 점차 감소했다. 또한, FA값의 감소비율은 NIH 뇌졸중척도와 Fugl–Meyer scale의 변화비용과 역의 상관관계를 보였다.$^{27,28}$

**Figure 2.** Secondary degeneration in the pyramidal tract and middle cerebellar peduncle after pontine infarction. A and B. Fluid-attenuated inversion recovery (FLAIR) image and diffusion tensor tractography (DTT), respectively. The white arrow indicates the pontine infarction site. The purple arrow indicates the degeneration of pyramidal tract superior and inferior to the infarction. The blue arrow indicates the degeneration of the ipsilateral middle cerebellar peduncle.
잠재적 치료 목표

이차변성은 뇌졸중 발생 이후 수주에 걸쳐 일어나기 때문에, 이 병변에 대한 치료 시간 창은 일차 뇌경색 영역에 대한 치료만큼 중요하다. 이차변성은 대상으로 한 치료방법의 개발은 아마도 뇌의 형성력(plasticity)을 증대시키고, 가능적 예후를 호전시킬 것이다. 사실, 증대뇌동맥 폐색이후의 이차변성은 실험실 연구에서 확인되었고(Figure 3), 여러 개의 치료가능 대상이 제시되어 왔다.

세포사멸(Apoptosis)

세포사멸을 시사하는 형태학적 변화, 즉 DNA 파편화, 핵항축(nuclear condensation), 세포사멸체(apoptotic bodies) 등이 백서에서 국소적 뇌경색 이후 동측의 시상에서 관찰되었고, Terminal deoxynucleotidyltransferase-mediated dUTP biotin nick end labeling(TUNEL)이 중추뇌 DNA 손상의 표지자이며, 증대뇌동맥 폐색 이후, terminal deoxynucleotidyltransferase-mediated dUTP nick end labeling(TUNEL)이 뇌경색 영역에서 관찰되었다. 

이러한 사실은 세포사멸이 아마도 시간의 이차변성에 관여할 것이라는 것을 시사한다. 또한, anti-apoptotic Bcl-2의 발현이 시상에서 감소했고, 유전자변형 생쥐 모델에서 Bcl-2의 과발현이 시상에서의 신경손상을 예방한다. 이 결과 또한 뇌경색 이후 이차변성에 세포사멸 방용이 관여할 가능성을 뿌받침한다.

Figure 3. Amyloid-beta (Aβ) deposits, neuronal loss, and glial activation in the ipsilateral thalamus at 14 days after middle cerebral artery occlusion in rats. A, Aβ immunostaining (star and arrow indicate infarct and Aβ deposits, respectively). NeuN (neuronal marker; B), GFAP (astrocytic marker; C), and OX42 (microglial marker; D) immunostaining, respectively. Scale bars in (A, B) apply to (A–D), respectively.
염증성 반응

인간의 몸에서, 시도키인의 상황 조절과 미세장세포/성 상세포 반응은 국소적 뇌도체 이후 병변과 열진 장소에서 나타나는 신경손상의 함께 또는 신경손상 깊이 중증 확인되어 왔다. 국소 뇌변성 이후 절여서 있는 양체에서의 염증반응에 대한 최근의 평론이나 이러한 면을 자세히 기술하였다. 염증성 반응은 이차 신경변성에서 조기 모양입니다. 뇌초의 시장에서, 중대뇌동맥 폐쇄 1일 이후에 tumor necrosis factor-α가 상장조정 되었고, 3일 후에 미세장세포/성 상세포 반응이 활성화되었다.  반면에, 신경변성은 중대뇌동

맥 폐쇄 4일 후에도 시작되었으며 14일이 지나야 되었다.  

일부 귀재들은 염증성 반응이 신경손상에 기여할 것이 

생각을 뒤받침한다. 활성화된 대식세포의 분비물인 osteopontin은 항염증작용을 통해 이차적 시장 병변에 대한 보호효과를 나타내는 것으로 보고되었다. 또한, 뇌 조직이 

이후 척수의 성장세포흡수(acstrocytic scarring)는 축삭 재생에 좋지 않은 환경을 만드는 것으로 생각되고 있다. 그럴듯이 불구하고, 일부 병변과 절여져 있는 지역의 신경손상에 대한 염증반응의 역할은 아직 완전히 밝혀지지 않았다. 염증반응이 단지 뇌병변의 결과인지 여부는 불명확하다.

신경독성, 신경약제인자

신경 독성, 신경약제 인자 또한 국소적 뇌도체 이후 이차 병변에 영향을 주는 것으로 보인다. 신경섬유의 후행성 그리고 진행성 변성이 아마도 공간적으로 열여져있는 뇌영역의 혈문 

독성일 인가로서 신경세포를 유도하는 것 같다. 예를 들어, 혈청의 글루토닌은 신경세포전달 GABA를 이용한 억제신호를 받고 신경하와로부터 glutamine 신호를 받는다. 신경세포 뇌 

손상에서는 혈청의 글루토닌의 억제 신호가 손상되어, 대사가 증가하고 신경세포가 발생할 것이다. 이 가설과 부합하게, MK-801 (glutamate N-methyl-d-aspartate receptor antagonist)와 YM872 (α-amino-3-hydroxy-5-methyl-

4-isoxazolpropionic acid receptor antagonist)로 치료 

했을 때 중대뇌동맥 폐쇄 이후 혈청 글루토닌의 이차변성이 감소 했다.  

알츠하이머병에서 노년판(seinline plaque)의 주된 구성요소인 Amyloid-beta (Aβ)는 신경독성물질로 알려져 있다. 중대뇌동맥 폐쇄 이후 9개월까지 동축 시장에서 Aβ가 비정상적으로 축삭되고 웅출하여 노년변과 비슷한 축삭물이 형성하였다. 저자들은 Aβ와 신경 이차변성의 관계에 대해 연구했고, functional γ-secretase 억제재를 투여했을 때 Aβ 축삭, 시장의 신경세포 소실이 유의하게 감소함을 확인했으며, 이는 Aβ 축삭이 시장의 이차변성과 관련되어 있을 것이라는 것을 시사한다. 


산화독성

DNA의 산화 독성은 일차 뇌도체의 신경손상에 역할을 할 뿐 아니라, 공간적으로 열여져 있는 뇌영역에서의 이차 신경변성의 발생과정에도 참여한다. 국소적 뇌도체 이후, 대인성 산화 

바이어직과 공간적으로 열여져있는 뇌영역에서 활성화된다. 백서의 중대뇌동맥 폐쇄 이후 동축의 시장에서 manganese-

superoxide dismutase의 변역반응이 증가하고 damage-induced neuronal endopidase mRNA의 발현이 증가하 

는 것이 관찰되었다. Superoxide dismutases는 효과적으 

로 활성을 얻고, 산화손상으로부터 신경을 보호한다고 알 

려져 있으며, damage-induced neuronal endopidase 

은 신경세포 손상에 반응해서 상황조절되고, superoxide 

dismutases를 활성화 시킨다. 그러므로, manganese-

superoxide dismutase의 증가와 damage-induced neu 

ronal endopidipades는 동축 시장의 산화 스트레스가 증가한 

 것을 반영한다.

백서를 이용한 저자들의 연구에서, 중대뇌동맥 폐쇄 이후 동 

축의 시장에서 8-hydroxy 2′-deoxyguanosine의 발현이 

증진되고 8-oxoguanine DNA glycosylase의 발현이 감소 

했다. 이는 DNS의 산화손상과 염기 치료 활성 비율 간의 불균 

형을 시사한다.  뿐만 아니라, 항산화제인 ebsele로 치료 

했을 때, 8-hydroxy-2′-deoxyguanosine 발현 증가를 의 

미 있게 약화시켰고, 8-oxoguanine DNA glycosylase 발현 

의 감소를 개선시켜, 동축 시장의 신경세포 손실을 줄였다. 

자식작용(Macroautophagy)

자식작용은 세포내기관과 단백의 재사용을 위한 용해소체 

경로로 세포 활성성유지에 많은 역할을 한다. 자식작용은 만성 

뇌질환에서는 세포 생존을 촉진할 수 있고, 급성 신경학적 질 

환에서 세포사를 증가할 수 있어서, 어떤 경우나에 따라 그 역 

할이 달라질 수 있다고 알려져 있다. 

저자들은 백서에서 대뇌피질의 뇌도체 이후 시장의 이차변 

성에서 자식작용의 역할에 대해 연구했으며, 자식작용이 동축 

시장의 세포에서 활성화된 것을 확인하였다.  뿐만 아니라, 자 

식작용의 역제제를 투여하거나 Beclin-1을 유전자로 억제 

시켰을 때 자식작용 활성화와 신경세포 소실을 유의하게 감소 

시켰고, 이는 아마도 자식작용이 시장의 이차변성에서 세포사 

에 역할을 할 것이라는 것을 시사한다. 이는 자식작용과 자식작용의 역할을 좀 더 이해하기 위해서는 자식작용이 어떻게
Sources of Funding

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Disclosures

None.

References


**KEY WORDS**: cerebral infarction ■ secondary neurodegeneration ■ computed tomography ■ magnetic resonance imaging ■ thalamus ■ pyramidal tract