Slowly progressive neuronal death associated with postischemic hyperperfusion in cortical laminar necrosis after high-flow bypass for a carotid intracavernous aneurysm

Case report

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The authors report a rare case of slowly progressive neuronal death associated with postischemic hyperperfusion in cortical laminar necrosis after radial artery/external carotid artery–middle cerebral artery bypass graft surgery for an intracavernous carotid artery aneurysm. Under barbiturate protection, a 69-year-old man underwent high-flow bypass surgery combined with carotid artery sacrifice for a symptomatic intracavernous aneurysm. The patient became restless postoperatively, and this restlessness peaked on postoperative Day (POD) 7. Diffusion-weighted and FLAIR MR images obtained on PODs 1 and 7 revealed subtle cortical hyperintensity in the temporal cortex subjected to temporary occlusion. On POD 13, 123I-iomazenil (123I-IMZ) SPECT clearly showed increased distribution on the early image and mildly decreased binding on the delayed image with count ratios of the affected–unaffected corresponding regions of interest of 1.23 and 0.84, respectively, suggesting postischemic hyperperfusion. This was consistent with the finding on 123I-iodoamphetamine SPECT. Of note, neuronal density in the affected cortex on the delayed 123I-IMZ image further decreased to the affected/unaffected ratio of 0.44 on POD 55 during the subacute stage when characteristic cortical hyperintensity on T1-weighted MR imaging, typical of cortical laminar necrosis, was emerging. The affected cortex showed marked atrophy 8 months after the operation despite complete neurological recovery. This report illustrates, for the first time, dynamic neuroradiological correlations between slowly progressive neuronal death shown by 123I-IMZ SPECT and cortical laminar necrosis on MR imaging in human stroke. (DOI: 10.3171/2009.9.JNS09345)

KEY WORDS  •  laminar necrosis  •  iomazenil  •  bypass  •  delayed neuronal death  •  magnetic resonance imaging

Cortical laminar necrosis is a permanent brain injury radiologically characterized by T1-weighted MR imaging–documented high-intensity cortical lesions that follow the gyral anatomy of the cerebral cortex.\textsuperscript{7,17,19} It has been associated with hypoxia, metabolic disturbances, drugs, infections, status epilepticus, and ischemic stroke.\textsuperscript{7,19} The neuropathological correlations, however, between neuronal loss and an emerging cortical T1 hyperintensity signal in human stroke remain unknown. Intracavernous CA aneurysms are usually treated by trapping with/without EC-IC bypass based on presumed tolerance to CA sacrifice.\textsuperscript{6,9} Flumazenil and iomazenil are markers of central benzodiazepine receptors, part of the GABAergic complex,\textsuperscript{2} and are ideal markers of perinftact tissue and incomplete brain infarcts.\textsuperscript{16} This is the first report illustrating slowly progressive neuronal death, shown by 123I-IMZ, during emerging cortical laminar necrosis on MR imaging after temporary occlusion at high-flow bypass for an intracavernous CA aneurysm.

Case Report

History and Examination. This 69-year-old man developed double vision and ptosis due to left oculomotor palsy. Angiograms obtained at the previous hospital showed bilateral large intracavernous CA aneurysms (Fig. 1A). After balloon test occlusion showing intolerance on temporary occlusion of the left CA, the patient was referred to our institution.

Operation. The patient’s left large CA aneurysm was trapped by RA/ECA-MCA bypass grafting without causing any neurological deficit. Temporary occlusion of the inferior trunk of M\textsubscript{2} was performed for 52 minutes under thiopental brain protection. Postoperative MR dif-

Abbreviations used in this paper: CA = carotid artery; EC-IC = extracranial-intracranial; ECA = external carotid artery; \textsuperscript{123}I-IMP = \textsuperscript{123}I-iodoamphetamine; \textsuperscript{123}I-IMZ = \textsuperscript{123}I-iomazenil; MCA = middle cerebral artery; POD = postoperative day; RA = radial artery.
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fusion weighted imaging demonstrated no abnormality. Two months later, the patient presented with contralateral oculomotor palsy due to progressive growth of the contralateral aneurysm. He underwent virtually the same operation, except with a shorter duration of temporary occlusion (47 minutes) and except for the observation that back flow from the distal M1 was slower and dark when the distal clip was first declamped after anastomosis, suggesting that the territory of the recipient artery had been subjected to ischemic insult due to insufficient collateral flow.

Postoperative Course. The patient awoke from anesthesia relatively soon without apparent neurological deficit. Diffusion weighted and FLAIR imaging on POD 1 showed slight cortical hyperintensity in the right temporal region (Fig. 1C and D). Angiograms obtained on POD 5 showed no opacification of the aneurysm and good bypass patency, but the patient gradually became restless. Diffusion weighted and FLAIR imaging repeated on POD 7 revealed similar findings (Fig. 1E and F). Because the signal change on diffusion weighted imaging, however, remained subtle, the cause of such MR imaging abnormality remained uncertain. Subtle Gd enhancement was noted in the temporal cortex. On POD 18, 123I-IMZ SPECT showed increased distribution on the early image (15 minutes) and decreased binding on the delayed image (3 hours) in the temporal region corresponding to the hyperintensity area on diffusion weighted and FLAIR images (Fig. 2). Because early and delayed images of 123I-IMZ SPECT represent the cerebral perfusion state and neuronal viability, respectively, these results clearly indicated that ischemic neuronal loss and posts ischemic hyperperfusion occurred as a result of ischemic insult by temporary occlusion during bypass surgery.

Chronological count ratio changes of the affected to the unaffected corresponding regions of interest on 123I-IMZ and 123I-IMP SPECT scans are shown in Fig. 3. In the temporal region subjected to temporary clipping, the affected/unaffected ratio on 123I-IMZ scans decreased during the subacute period between PODs 18 (ratio 0.84) and 55 (ratio 0.44), and then it leveled off later (ratio 0.43 on POD 239), whereas it remained relatively constant in other regions. We did not obtain 123I-IMZ SPECT scans before the operation. On 123I-IMP SPECT, the affected/unaffected ratio transiently increased during PODs 13 (ratio 1.21) and 26 (ratio 1.23), and it progressively decreased on PODs 53 (ratio 0.84) and 236 (ratio 0.67) in the temporal region, although virtually no changes were noted in other areas.

Correlation of SPECT and MR Imaging Findings. Serial FLAIR images showed cortical hyperintensity, which appeared on POD 1, peaked during PODs 7 and 13, almost returned to normal on POD 56, and demonstrated atrophy in the right temporal lobe on POD 237 (Fig. 4). During transient hyperperfusion and chronic hyperperfusion stages, 123I-iodoamphetamine FLAIR demonstrated marked cortical edema and chronic atrophic change of the affected region, respectively. Subtle diffusion weighted imaging hyperintensity in the affected area was shown between PODs 1 and 7 but disappeared on POD 35, despite slowly progressive neuronal death documented on 123I-IMZ in the subacute phase (PODs 18–55), during which T1 cortical hyperintensity became prominent (PODs 35–56). The hyperperfusion state of the affected cortex was also confirmed by 123I-IMP SPECT on POD 12. Hyperperfusion of the affected cortex gradually improved and returned to normal, as shown by 123I-IMP SPECT on POD 53. Follow-up MR images showed unique chronological changes such that cortical hyperintensity of the affected cortex appeared on POD 35 and persisted at least until POD 56. Of note, cortical hyperintensity on FLAIR peaked on POD 7 and then gradually decreased in intensity and appeared almost normal on POD 56. In the late chronic stage on POD 237, cortical atrophy with secondary degeneration of the underlying subcortical white matter was noted. No hemorrhagic transformation was noted in the affected regions on CT scans throughout the observation period.

Follow-Up. The patient’s cranial nerve III palsy and restlessness gradually improved and he resumed his previous lifestyle 5 months after the second surgery. Eight months after surgery, his Mini-Mental State Examination status returned to normal.

Discussion

We have presented, for the first time, dynamic neuroradiological correlations between slowly progressive neuronal death during posts ischemic hyperperfusion, as shown on 123I-IMZ and 123I-IMP SPECT scans, and emerging cortical laminar necrosis, as shown on T1-weighted MR images, after RA/ECA-MCA bypass grafting for an intracavernous CA aneurysm.

Intracavernous CA aneurysms are usually treated by trapping with/w without EC-IC bypass based on presumed tolerance to CA sacrifice.9 If the CA does not tolerate the balloon test occlusion, a high-flow bypass is indicated when CA sacrifice is performed. Creation of an RA/ECA-MCA bypass graft is a common method of high-flow bypass, and the technical standards and pitfalls have been reported previously.9,12 The incidence of ischemic complications has been reported to be ~10%, as a result of early graft occlusion and other causes, but the underlying etiological force, most of which has been considered thromboembolic, remains unproven in most cases.6,9

Cortical laminar necrosis is a permanent brain injury characterized on T1-weighted MR images by high-intensity cortical lesions that follow the gyral anatomy of the cerebral cortex. Histopathological and experimental animal studies have demonstrated much more vulnerability of the gray matter than white matter to ischemic necrosis due to hyperperfusion.9,19 Previous studies have reported characteristic MR imaging findings of cortical laminar necrosis caused by hypoxic or ischemic brain damage.7,19 Cortical enhancement on postcontrast T1-weighted images in the subacute stage, suggesting breakdown of the blood-brain barrier, and hyperintense cortical lesions on unenhanced T1-weighted images during the late subacute and early chronic stages were reported to be distributed in the laminae. Cortical laminar necrosis is usually reported...
to be associated with volume loss of the affected cortex in the chronic stage.\textsuperscript{20} Weiller and coworkers\textsuperscript{20} have reported finding atrophy of the opercular cortex overlying the subcortical infarct on follow-up MR images ~ 1 year after the insult, suggesting that neuronal loss progresses over time.\textsuperscript{13,20} In the present case we observed similar chronological changes of MR imaging signals on T1-weighted and FLAIR images and clearly illustrated the dynamic process of slowly progressive neuronal death associated with postischemic hyperperfusion in the affected cortex, where cortical hyperintensity was emerging in the subacute phase, following subtle diffusion weighted imaging–documented abnormalities in the acute phase.

Hyperperfusion is defined as a significant increase in cerebral blood flow relative to the homologous area of the contralateral hemisphere,\textsuperscript{10} and it is known to occur after carotid endarterectomy, EC-IC bypass, and giant aneurysm clipping in patients with chronically impaired cerebrovascular reserve. Previous studies that involved the use of PET or SPECT scanning suggest that hyperperfusion may sometimes be associated with incomplete infarction or selective neuronal loss.\textsuperscript{3,13} Flumazenil and $^{123}$I-IMZ are markers of central benzodiazepine receptors, part of the GABAergic complex,\textsuperscript{2} and ideal markers of periinfarct tissue and incomplete brain infarcts.\textsuperscript{16} Sette et al.\textsuperscript{16} have reported marked hyperperfusion in the affected territory in ischemic stroke, together with mildly reduced binding of $^{11}$C-flumazenil in the acute stage, followed by reduced $^{11}$C-flumazenil binding and reduced cerebral metabolic rates of glucose despite unaltered MR imaging findings in the subacute stage. Nakagawara and colleagues\textsuperscript{13} have also reported using $^{123}$I-IMZ SPECT in 2 patients with extensive hyperperfusion in the acute stage who exhibited reduced binding of $^{123}$I-iomazenil in these areas in the chronic stage despite normal CT findings. The degree and duration of moderate ischemia in the present case was probably in the narrow range, which caused slowly progressive neuronal death without the development of frank infarction involving subcortical white matter, as reported in transient ischemia in animal models.\textsuperscript{1} In internal carotid artery occlusive disease, selective neuronal damage was reported to occur beyond the regions of infarcts by hemodynamic ischemia in the chronic stage, as demonstrated on $^{11}$C-flumazenil PET scans.\textsuperscript{22}

The diagnostic significance of diffusion weighted imaging deserves some mention. Diffusion weighted imaging is considered an accurate predictor of the extent of infarction during the acute or early subacute phase of cerebral ischemia. Heiss et al.\textsuperscript{4} compared the probability of cortical infarction by examining flumazenil binding on PET and diffusion weighted images in early ischemic stroke; they concluded that these modalities are comparable in predicting the probability of ischemic cortical infarction. Benzodiazepine receptor activity is a reliable marker of neuronal integrity in the cortex, but movement of water molecules in the extracellular space may be a more variable indicator of tissue damage, such that the false-positive volumes not included in the final infarct were larger for diffusion weighted imaging.\textsuperscript{4} Subtle cortical hyperintensity on diffusion weighted imaging of the

**Fig. 1.** A: Three-dimensional rotational CA angiogram showing a large intracavernous aneurysm that was treated with radial artery/ECA-MCA bypass grafting. B: Postoperative angiogram. C and D: Diffusion weighted (C) and FLAIR (D) images obtained on POD 1, showing only subtle hyperintensity in the right temporal cortex subjected to temporary clipping. E and F: Diffusion weighted (E) and FLAIR (F) images obtained on POD 7 when the patient became restless. Both of the hyperintensities following a gyral pattern appear slightly increased and well demarcated. Arrows indicate the affected region in the temporal lobe.
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affected cortex on PODs 1 and 7 in this case, as reported in global ischemia,11 disappeared thereafter, despite ongoing neuronal loss during the subacute stage. In animal models, modest signal intensity changes on diffusion weighted imaging precede delayed neuronal necrosis after transient ischemia.15 In the present case, however, the rate of decrease of the affected/unaffected ratio, as seen on the delayed 123I-IMZ images, remained constant until POD 55 before and after the first postoperative 123I-IMZ image, if the affected/unaffected ratio before surgery in

Fig. 3. Line graphs depicting chronological changes of the affected/unaffected count ratio and corresponding regions of interest on delayed 123I-IMZ (left) and 123I-IMP (right) SPECT images. The count ratio of the affected/unaffected corresponding regions of interest of 123I-IMZ in the different areas (temporal, precentral, occipital, and cerebellar regions) are plotted against PODs. The affected/unaffected ratio of 123I-IMP was plotted only for the affected temporal region.
the affected cortex was assumed to be 1.0, as in the other areas on the first postoperative $^{123}$I-IMZ image. These findings suggest that neuronal loss may not be of delayed onset, but rather slowly progressive after surgery, and diffusion weighted and $^{123}$I-IMZ imaging may differ in predicting the probability of slowly progressive neuronal death in cortical laminar necrosis, depending on the interval from the moderate ischemic insult. Iodine-123–labeled IMZ SPECT is useful for examining the dynamic process of slowly progressive neuronal loss, especially in the subacute phase after moderate ischemia. Precise understanding of temporal profiles of neuronal death underlying emerging cortical laminar necrosis should require further accumulation of evidence using $^{123}$I-IMZ SPECT. Previous studies discussed the time permitted for temporary occlusion of the parent artery for aneurysm surgery, especially for an MCA bifurcation aneurysm. In radial artery/ECA-MCA bypass grafting, however, the time permitted for temporary occlusion of the M$_2$ segment remains unclear, although the anastomotic time has been recommended to be less than 45 minutes. Obviously, the time threshold for temporary occlusion may depend on multiple factors, such as the use of various neuroprotective agents, brain temperature, and extent of collateral flow and cerebrovascular reserve. During the previous 6 years, neither isolated cortical laminar necrosis nor frank infarction due to temporary occlusion had been documented in the other 21 cases treated by high-flow bypass, including 10 patients in whom temporary occlusion lasted more than 45 minutes. In the present case, extremely slow backflow from the distal side of the clamped artery was a key intraoperative finding, underlying the development of slowly progressive neuronal death. Although previous studies have reported possible preventative measures of ischemic complications related to temporary occlusion, such as excimer laser–assisted nonocclusive anastomosis, the development of small intravascular shunts, and double insurance bypass, there are no widely accepted methods for this purpose.

**Conclusions**

We have discussed a rare case of slowly progressive neuronal death during postischemic hyperperfusion in cortical laminar necrosis associated with radial artery/ECA-MCA bypass grafting for intracavernous CA aneurysms. We have illustrated the diagnostic importance of 123I-IMZ SPECT in the subacute phase before emerging characteristic MR imaging findings. Moderate ischemia during temporary occlusion due to poor collateral flow may cause this rare ischemic complication.

**Disclaimer**

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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References


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