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Intracranial Atherosclerosis: Incidence, Diagnosis and Treatment

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Intracranial atherosclerosis is considered a cause of approximately 8% of all strokes in the western society. However, its frequency is much higher in Asian countries. In our hospital-based study, among the patients who had angiographic abnormalities, the frequency of intracranial atherosclerosis was approximately 70% far exceeding that of extratracranial atherosclerosis. Symptomatic atherosclerotic diseases were most often found in the middle cerebral artery. Generally, it has been shown that obesity and hyperlipidemia are related to extracranial diseases while advance hypertension is associated with intracranial diseases. However, these results have not always been replicated, and certain genetic factors may be related with the ethnic differences in the location of atherosclerosis. Recent studies using diffusion weighted MRI showed that the main mechanisms of stroke in patients with intracranial atherosclerosis are the branch occlusion, artery to artery embolism and both. The intracranial stenosis, especially symptomatic one, is not a static condition and may progress or regress in a relatively short period of time. Progressive stenosis of intracranial arteries is clearly related to the development of ischemic events. The annual risk of stroke relevant to the stenosed intracranial vessel is approximately 8 %. In retrospective studies including WASID, anticoagulation was found to be superior to aspirin in reducing the stroke events. However, a recent prospective study failed to confirm the superiority of anticoagulation over aspirin in patients with intracranial stenosis. Moreover, anticoagulation resulted in excessive central nervous system bleeding as compared to aspirin. Because aspirin alone seems to be insufficient in the prevention of progression of intracranial stenosis, a combination of antiplatelets has been tried. Recently, we found that a combination of aspirin + cilostazol was superior to aspirin monotherapy in the prevention of progression of symptomatic intracranial stenosis. However, further studies are required to find out the best combination of antiplatelets for symptomatic intracranial stenosis. The effect of other atheroma stabilizers such as statins should also be properly evaluated. Angioplasty/stent is another important option for the relatively severe intracranial stenosis. According to previous studies, immediate success rate has reached up to 90%. If patients are carefully selected, and procedures done by experienced hand, angioplasty/stent can be of benefit especially in relatively young patients with proximal, short-segment, severe symptomatic stenosis. However, this procedure is not without complications or long-term re-stenosis. Further studies are required to elucidate the best therapeutic strategy in patients with intracranial atherosclerosis.
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INCIDENCE AND RISK FACTORS

Intracranial atherosclerosis (IAS) has been shown to be an uncommon cause of stroke in western society occurring in approximately 8% of patients with ischemic stroke or transient ischemic attack.[1] This is especially a rare occurrence among Caucasians; according to the Northern Manhattan Stroke Study, only 1% of white patients suffered a stroke that was caused by an IAS.[2]

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However, angiographic[3-6] or pathologic[7] studies have shown that the prevalence of IAS is much higher in Blacks and Asians. Moreover, because lacune-like small subcortical infarction can be caused by IAS,[8] and this may be regarded as a small vessel disease unless angiogram is routinely used, the prevalence of IAS is likely to be underestimated. In our institute, where approximately 90% of admitted patients underwent angiogram (mostly, MR angiogram), IAS is more common than extracranial atherosclerosis with an approximate ratio of 7:3. Symptomatic atherosclerosis most often occurred in the middle cerebral artery (MCA) (38%) which was followed by internal carotid artery (28%, extracranial carotid artery disease in 15%).

The risk factors for IAS include hypertension, diabetes mellitus, cigarette smoking and hyperlipidemia. There have been debates about possible differences in risk factors between intracranial and extracranial diseases. Advanced hypertension has been shown to be a risk factor preferentially related to the former, while obesity and hyperlipidemia were regarded as important factors related to the latter.[9] However, our previous study failed to find differences in risk factors between intracranial and extranial atherosclerosis.[10] Inzitari et al also found that ethnicity was still a significant factor determining the site of atherosclerosis after adjusting various risk factors.[11] Perhaps, differences in certain genetic predisposition or morphological characteristics of the cerebral vessels may explain the difference in the incidence of IAS among different ethnicities.

DIAGNOSIS

For the diagnosis of IAS, conventional angiogram, MR angiogram (MRA), CT angiogram (CTA), and transcranial dopper (TCD) are widely used. Studies comparing MRA, CTA or TCD with catheter angiography have shown fairly high diagnostic sensitivity and specificity.[12,13] However, there has been no standard method for measuring the severity of IAS because established methods for measuring extracranial carotid stenosis may not be suitable for the IAS. Recently, a standardized method for measuring IAS was developed for Warfarin-Aspirin Symptomatic Intracranial Disease (WASID) trial.[14] Based on WASID measurement criteria, percent stenosis was defined as $[(1-(D_{stenosis}/D_{normal}))]X100$, where $D_{stenosis}$ = the diameter of the artery at the site of the most severe stenosis and D_{normal} = the diameter of the proximal normal artery. If the proximal segment was diseased, the contingency sites were chosen to measure Dnormal: distal artery (second choice) or feeding artery (third choice). This method showed good interobserver and intraobserver agreements.

The diagnosis of IAS is sometimes challenging, particularly during the early post-stroke period. In this stage, it is difficult to differentiate intrinsic atherosclerotic disease from an embolic occlusion. In most previous studies including WASID trial,[15] IAS was diagnosed if there was stenosis more than 50% or occlusion without the presence of cardioembolic sources. However, complete cardiac work-up cannot be performed in all stroke patients. Moreover, cardioembolic mechanism cannot be completely excluded even if there is no definite abnormality in cardiac evaluation. In our preliminary data, among 53 patients with acutely diagnosed IAS (>50% or occlusion) detected by MRA, significant recanalization was achieved in 20 patients on follow-up MRA performed within a week of stroke onset. However, embolic sources from the heart or proximal arteries were not identified in 6 of those 20 patients. Our data suggest that IAS may be overestimated in the acute stage and that follow-up vascular investigation is necessary for the proper evaluation of IAS.

It is well known that plaque vulnerability is more important than the degree of stenosis in the evolution of myocardial infarction. Therefore, it is not uncommon to see the development of myocardial infarction in patients with only mild or moderate coronary stenosis.[16] Although it is still unclear whether coronary-like plaque rupture occurs in the IAS, there has been suggestion that similar phenomenon occurs in the IAS as well.[17] Nevertheless, current imaging modalities have limitations in the identification of plaque characteristics of IAS. Moreover, an intact lumen observed by angiogram studies does not always indicate the absence of IAS. Future novel imaging techniques such as high resolution

MRI may reveal atherosclerotic wall changes that do not make luminal stenosis.[18]

PATHOLOGY AND STROKE MECHANISMS

Pathological studies on the IAS have been rare. The progression of atherosclerosis includes the stage of a fatty streak and that of a fibrous plaque. There has been suggestion that plaque morphology rather than the degree of stenosis may be more important in clinical events. The rupture of the unstable plaque, which is a large lipid core and a thin fibrous cap with evidence of inflammation, may cause the subsequent thrombosis and the ischemic stroke in patients with IAS.[17]

The lesion patterns and stroke mechanism caused by IAS are also understudied. In a recent study using diffusion weighted MRI (DWI) and TCD in 30 acute stroke patients with MCA stenosis, common stroke mechanisms were the occlusion of a single penetrating artery to produce a small subcortical lacune-like infarct or artery-to-artery embolism to produce multiple cerebral infarcts.[19] The authors also found that the number of microembolic signals predicted the number of acute infarcts detected on DWI. A high frequency (50%) of multiple acute infarcts on DWI in their study suggests that embolism is a common underlying mechanism in patients with MCA stenosis. Microembolism in cortical branches distal to MCA stenosis was also documented histopathologically.[20]

A single, small subcortical perforator infarct is also common in MCA stenosis. In these patients, the atheroma in the MCA seems to occlude the origin of a penetrating artery leading to a lacune-like infarct.[21] In our recent study using DWI and MRA, there was no difference in the lesion size between the subcortical lesions associated with MCA disease and those without. Therefore, the 1.5 cm size criteria for `small vessel disease' may be no longer valid.[22] According to our data, there also was no difference in clinical features between the two groups. However, another recent study suggested that small, deep infarcts associated with atherosclerotic MCA disease are related with unstable clinical courses.[23] The rate of stroke recurrence in patients with a parent arterial lesion may also be higher than that in those with small artery disease.[8]

According to our data using DWI performed within 48 hours of onset in 66 patients with MCA disease,[24] the most common lesion pattern was multiple infarcts involving both perforator and pial territories (n = 22), which were followed by single small (<2 cm) perforator infarct (n = 12). Our data suggest that thrombotic and embolic mechanisms frequently coexist in the pathogenesis of infarcts in patients with atherosclerotic MCA disease.

NATURAL COURSE

Previous studies have shown that IAS is a dynamic process with frequent progression or regression. In a retrospective study of 21 patients with 45 IAS, who underwent repeated angiography at an average interval of 26.7 months, intracranial internal carotid artery was relatively stable (20% progressed, 14% regressed) while stenosis occurring in the MCA, ACA or PCA was unstable (61% progressed, 28% regressed).[25] Another study reported that among 40 MCA stenosis, 33% progressed and 7.5% regressed during 26.6 months of follow up.[26] According to our results, the progression of symptomatic MCA stenoses (17/82, 20.7%) was more frequent than that of asymptomatic ones (3/60, 5%).[27] Moreover, the progression of MCA stenosis was an independent predictor for clinical stroke recurrence.26 Therefore, symptomatic IAS requires more aggressive therapeutic intervention than asymptomatic one.

The natural course of IAS is likely to be influenced by risk factor modification. In addition, there has been suggestion that certain inflammatory or angiogenic factors are related to the natural course. A previous study showed that C-reactive protein (CRP), an inflammatory marker, was an independent factor for the progression of IAS as well as clinical recurrence.[28] A more recent study[29] measured the blood level of pro-angiogenic vascular endothelial growth factor (VEGF) and the anti-angiogenic endostatin in patients with symptomatic IAS. The authors attempted to see whether the levels of these proteins were related to the

extent of IAS and the risk of stroke recurrence. They found that endostatin/VEGF ratio was independently associated with a greater extent of IAS. A higher level of endostatin was also a predictor for new stroke events. These results suggest that a predominance of the angiogenic inhibitor endostatin is associated with a greater extent of IAS and a higher risk of stroke recurrence in patients with symptomatic IAS.

MANAGEMENT

Based on the retrospective results suggesting the advantage of warfarin over antiplatelet agents,[30] a prospective WASID trial was performed. The study compared the efficacy of warfarin (INR 2-3) with that of aspirin (1300 mg/day) for preventing stroke and vascular death in patients with significant (more than 50%) symptomatic IAS. This WASID trial was prematurely terminated by the NINDS following the recommendation of the Safety Monitoring Committee because of higher hemorrhagic rates than expected in the warfarin arm.[31] Although this trial attempted to show a 30% risk reduction of warfarin against aspirin, it showed only a slight trend favoring warfarin at about 1.7 years of follow-up. Moreover, according to the Warfarin Aspirin Recurrent Stroke Study (WARSS) which recruited 2206 patients,[32] 149 patients (13.5%) in the warfarin arm developed recurrent ischemic stroke, while 123 (11.2%) in the aspirin arm developed strokes at about 2.1 years of follow up. For large artery stroke, the primary events (death or recurrent ischemic stroke) occurred more often in patients on the warfarin (18.7%) than those on the aspirin (15.6%). Therefore, oral anticoagulation is nowadays not recommended in patients with symptomatic IAS. Nevertheless, there still is a lingering argument that using anticoagulation in the early stage of stroke may be beneficial especially in patients with a presumed high risk of recurrence.

According to the EC-IC bypass trial, the annual risk of stroke in the aspirin arm was unacceptably high in patients with IAS reaching to 7.7-9.5%.[33] Therefore, a combination of antiplatelet agents with different mechanism of action has been considered. The synergistic effect was indeed present when aspirin (a cyclo-oxygenase inhibitor) and clopidogrel (inhibitor of ADP-induced platelet aggregation) were combined in patients with acute coronary syndrome34 or in those who underwent percutaneous coronary intervention.[35]

European Stroke Prevention Study 2 (ESPS-2) revealed that a combination of aspirin (a cyclo-oxygenase inhibitor) and dipyridamol (phosphodiesterase inhibitor) was significantly more effective than when either agent was prescribed singly in the secondary prevention of stroke.[36] However, it remains unknown whether this combination is superior to monotherapy in patients with IAS. Moreover, recent studies have suggested that two is not always better than one. MATCH (Management of ATherothrombosis with Clopidogrel in High-risk patients) was a trial expected to show a beneficial effect of the combination of aspirin and clopidogrel over clopidogrel monotherapy in patients with ischemic stroke. In this trial, adding aspirin only slightly (insignificantly) reduced the incidence of ischemic stroke, myocardial ischemia, or vascular death. Furthermore, the benefit was offset by life threatening hemorrhages into the gastrointestinal tract or brain in patients with combined treatment.[37] The unexpected results may be related with the inclusion of unusually large proportion of lacunar strokes; it has been shown that lacunar infarction is related to a relatively high risk of subsequent intracerebral hemorrhage, and a low risk of recurrent stroke as compared to those with stroke due to large vessel atherosclerosis. Therefore, it remains unclear whether the combination of aspirin and clopidogrel is superior to aspirin or clopidogrel monotherapy in patients with IAS.

Recently, we have considered combining aspirin with cilostazol, a phosphodiesterase III inhibitor. Cilostazol has an antipletelet as well as vasodilating effects, and has been shown to be effective in the symptomatic improvement for the intermittent claudication[38] and in the prevention of restenosis after coronary angioplasty and stenting.[39] In our trial, we studied 135 patients with acute symptomatic IAS. The patients were randomly treated with either cilostazol 200 mg a day or placebo for 6 months. Aspirin 100 mg per day was also given to all patients. MRA and TCD were performed at <2

weeks and at 6 months after stroke onset, and the change of the initial stenosis was assessed. In the aspirin + cilostazol group, IAS progressed in 3 and regressed in 11 out of 45 arteries whereas in the aspirin group, it progressed in 15 and regressed in 8 out of 52 arteries. The progression rate of symptomatic IAS was significantly lower in the ciostazol+aspirin than in aspirin monotherapy group (p=0.018).[40] Because of the short term follow up, we were not able to see the actual reduction of clinical events by the combined treatment. However, considering previous results that the progression of IAS is related to clinical recurrence[26,41] the combined treatment seems to be of benefit in the reducing the recurrence of ischemic strokes as well.

Nevertheless, we do not know whether the aspirin + cilostazol combination is superior to other types of combination. In addition, there still are other drugs that may be beneficial in patients with IAS. In a recent trial, there was a tendency of the less progression of IAS in patients who received statin as compared to those receiving a placebo. However, this did not reach to a statistical significance. Instead, statin use was effective in reducing the development of white matter signal intensities detected by MRI.[42] Therefore, further studies are required to elucidate what is the best medical treatment for the IAS.

The IAS may be managed by non-medical ways of treatment. Percutaneous transluminal angioplasty and stenting (PTA) for the IAS should be considered as a complementary treatment to reduce the risk of ischemic stroke. We personally experienced that intractable TIAs improved after the PTA. However, because there have been no randomized clinical trials to prove its benefit, PTA should be carefully performed in appropriately selected patients. Technical successful rates of the reported cases were usually high (85-98%), but the complication of the PTA is not uncommon (10-33%).[43-46] Urgent PTA is related with even higher major neurological complication (50%) and mortality rate (16.7%).[47] The results of Stenting of Symptomatic Atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA)[48] were more promising than previous reports. The procedure-related stroke rate was very low (6.6%) and technical successful rate was fairly high (95%). However, restenosis rate was high (32.4%), which was related with relatively frequent (39%) clinical events. Currently, we consider PTA for IAS in patients with symptomatic, medically intractable, technically feasible (proximal, short segment) and severe (>50%) IAS. In our experiences with 35 symptomatic patients, angiographic success rate was 97% and there were four procedure-related complications (11%) including a death and a minor stroke. During the average of 22 months follow up, restenosis occurred in five (15%) in the target vessels (symptomatic in 2, and asymptomatic in 3).[49] More researches are required to improve the results of PTA.

Finally, extracranial-intracranial artery bypass surgery is another option for the severely stenosed or occluded intracranial arteries. Although previous EC-IC bypass trial failed to show any benefits,[33] this procedure may still be of value in highly selected patients. Considering the results of the Japanese EC-IC bypass trial,[50] bypass surgery may help the patients with symptomatic IAS associated with hemodynamically compromised status.[51]

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