Illustrative Teaching Case

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Diagnosis and Management of Active Intracranial Atherosclerotic Disease

A Case Study

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A 68-year-old man with a past medical history of hypertension and hyperlipidemia was admitted with dizziness and right-sided weakness. Neurological examination revealed mild right hemiparesis but was otherwise normal. The initial brain magnetic resonance imaging (MRI) was negative for any acute abnormalities; magnetic resonance angiography showed irregularity of the right intracranial vertebral artery with mild stenosis (Figure 1A). A follow-up brain MRI confirmed a left pyramidal stroke. He was discharged to an inpatient rehabilitation facility on aspirin and high-intensity statin therapy.

One year later, he was admitted for transient visual distortion and dizziness which lasted 15 minutes. Neurological examination noted mild right hemiparesis with no other new findings. MRI brain revealed a small acute left cerebellar infarct (Figure 1B) and magnetic resonance angiography of the head and neck demonstrated worsening atherosclerosis in the right intracranial vertebral artery with severe stenosis and interval occlusion of the left intracranial vertebral artery (Figure 1C). Aspirin was switched to clopidogrel monotherapy and statin therapy was maintained. Two days after discharge, he was readmitted for transient dizziness and imbalance lasting 30 minutes. His examination had returned to baseline on hospital arrival. Repeat MRI of the brain showed new small acute bilateral cerebellar infarcts and a punctate right occipital acute infarct (Figure 1D). Magnetic resonance angiography of the head with vessel wall imaging of the vertebral arteries showed enhancement within the wall of the left vertebral artery suggestive of an active atherosclerotic plaque; MRI perfusion with RAPID processing revealed a region of moderate volume with Tmax delay (4–6 s) but no regions with Tmax > 6 s (Figure 2A through 2C). Aspirin was switched to clopidogrel monotherapy and statin therapy was maintained. Two days after discharge, he was readmitted for transient dizziness and imbalance lasting 30 minutes. His examination had returned to baseline on hospital arrival. Repeat MRI of the brain showed new small acute bilateral cerebellar infarcts and a punctate right occipital acute infarct (Figure 1D). Magnetic resonance angiography of the head with vessel wall imaging of the right intracranial vertebral artery (Figure 1C) showed enhancement within the wall suggestive of an active atherosclerotic plaque; MRI perfusion with RAPID processing revealed a region of moderate volume with Tmax delay (4–6 s) but no regions with Tmax > 6 s (Figure 2A through 2C) and normal cerebral blood flow and cerebral blood volume. Transcranial Doppler (TCD) with microemboli detection of the basilar artery was positive for high-intensity transient signals (Figure 2D). As a result, he was started on dual antiplatelet therapy with aspirin and clopidogrel (for 6 months and then transitioned to single agent) in addition to high-intensity statin therapy. He was followed for 2 years without recurrent events.

Discussion

Intracranial atherosclerotic disease (ICAD) is a major cause of ischemic stroke worldwide with a predilection for Asian, Black, and Hispanic populations. The middle cerebral arteries are most commonly affected, followed by the basilar artery, the internal carotid arteries, and the vertebral arteries. Risk factors for ICAD include age, hypertension, hyperlipidemia, and diabetes mellitus. Mechanisms of stroke in patients with ICAD include impaired distal perfusion and plaque rupture leading to distal embolization or branch occlusive disease.

Imaging modalities available to diagnose and quantify ICAD include computerized tomographic angiography, magnetic resonance angiography, TCD, and catheter angiography, which is considered the gold standard modality. Because catheter angiography is an invasive procedure with a small risk of stroke and does not necessarily change management; noninvasive modalities are the preferred screening tools. Additionally, MR vessel wall imaging can be used to identify wall pathologies including active atherosclerotic plaque because gadolinium enhancement correlates with fibrous cap rupture in histological samples, thus suggesting an increased risk of an ischemic event.

ICAD is associated with an increased risk of early ischemic stroke recurrence. In the WASID trial (Warfarin–Aspirin Symptomatic Intracranial Disease), factors associated with increased risk of stroke recurrence in patients with symptomatic ICAD were severe stenosis (>70%) and poor collaterals which reflect distal perfusion status. In WASID, the risk of recurrent stroke or death was 25% at 1 year with the highest risk being in the first 30 days (10.7%) after the initial event. In fact, recent evidence suggests that impaired distal perfusion confers an increased risk of recurrent stroke despite maximal medical therapy in patients with symptomatic ICAD, particularly in patients with the vertebrobasilar disease. Besides impaired distal perfusion, detection of high-intensity transient signals on TCD is another marker of an active atherosclerotic plaque that predicts stroke risk in patients with asymptomatic carotid stenosis and therefore identifying these in the setting of ICAD may potentially be another determinant of stroke risk.
risk. The ongoing MYRIAD study (Mechanisms of Early Recurrence in Intracranial Atherosclerotic Disease) is assessing which mechanisms exert the greatest risk and their interactions using a multimodal imaging protocol (URL: http://www.clinicaltrials.gov. Unique identifier: NCT02121028).

Antithrombotics, statin therapy, and risk factor modification are the mainstays of management in patients with symptomatic ICAD. The commonly used antithrombotic medications include aspirin, clopidogrel, a combination of aspirin and dipyridamole, ticagrelor, and cilostazol. Dual antiplatelet therapy for 3 months with an eventual transition to a single agent may confer increased protection from early recurrent stroke. In the CLAIR study (The Clopidogrel Plus Aspirin Versus Aspirin Alone for Reducing Embolization in Patients With Acute Symptomatic Cerebral or Carotid Artery Stenosis), which randomized stroke patients with symptomatic intracranial or extracranial atherosclerotic disease to receive daily aspirin alone versus daily aspirin plus daily clopidogrel (after a loading dose), the dual antiplatelet group had a lower rate of microemboli signal detection on TCD on day 2 and day 7 when compared with the aspirin-only group. Therefore, the use of dual antiplatelet therapy for up to 3 months followed by a single agent may be considered especially in the setting of an active symptomatic atherosclerotic plaque as evident by positive high-intensity transient signals on TCD or plaque enhancement on vessel wall imaging. Long-term dual antiplatelet therapy, however, for stroke prevention has not been shown to reduce the risk of recurrent stroke and was associated with increased hemorrhagic complications.

To date, there is no evidence to support endovascular therapy in ICAD population. The SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) randomized patients with recent transient ischemic attack or a nondisabling stroke attributable to severe stenosis (>70%) of an intracranial artery to percutaneous transluminal angioplasty and stenting with...
medical management versus medical management alone. Medical management included dual antiplatelet agents for 90 days followed by a single agent, intensive vascular risk factor modification (target blood pressure <140/90 mmHg and <130/80 in diabetics; LDL [low-density lipoprotein] <70 mg/dL), and lifestyle changes with the help of a lifestyle modification program (smoking cessation, weight loss, and exercise program). Enrollment was halted because of the significantly higher risk of stroke or death in the percutaneous transluminal angioplasty and stenting group, a finding also confirmed in the VISSIT study (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy). Interestingly, the event rate in medically treated patients in the SAMMPRIS trial (5.8% at 30 days and 12.2% at 1 year) was lower than historical cohorts, particularly those from the WASID trial (10.7% at 30 days and 25% at 1 year). This was attributed to significant advances in medical treatment over the past decade and the medical management arm of SAMMPRIS including a comprehensive approach using statins, antihypertensive agents, and lifestyle modifications in addition to antithrombotic agents. One limitation of these studies, however, was that they did not select patients with a hemodynamic mechanism where we hypothesize medical treatment is more likely to fail, and endovascular treatment is more likely to be of benefit. Future studies are needed to investigate the effectiveness of endovascular treatment in patients with symptomatic ICAD and impaired distal perfusion.

TAKE-HOME POINTS

- Intracranial atherosclerotic disease is an important cause of ischemic stroke worldwide.
- Intracranial atherosclerosis is associated with an increased risk of early recurrence.
- Vessel wall imaging, transcranial Doppler with microemboli detection, and perfusion imaging may further stratify recurrent stroke risk in patients with symptomatic intracranial atherosclerosis.
- Antiplatelet agents, including short-term dual antiplatelet therapy, high-intensity statin therapy, and risk factor modification are the mainstays of treatment.
- Clinical trials investigating the efficacy of endovascular treatment in patients with intracranial atherosclerosis and impaired distal perfusion are needed.

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Disclosures

None.

References


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