Intracranial Atherosclerotic Disease:
Epidemiology, Imaging and Treatment

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Over the past decade, there has been a marked awareness of the epidemiology, clinical severity and treatment options for patients with **Intracranial Atherosclerotic disease (ICAD)**. Once thought to be uncommon, it is now known that ICAD is almost as common as extracranial (cervical) carotid atherosclerotic disease. In addition, it is known which subgroups that are at the highest risk of subsequent stroke. While the optimal treatment paradigm for ICAD is unknown, endovascular techniques (angioplasty and stenting) can be safely done that may reduce stroke rates in appropriately selected patients. In this article, we review the epidemiology, natural history, imaging, and treatment of ICAD.

Epidemiology

ICAD accounts for approximately 5 to 10% of all strokes and **transient ischemic attacks (TIAs).**[1] Among the more specific studies, the German Stroke Study Collaboration prospectively identified 4157 patients over 20 months at 11 different centers who were admitted within 24 hours of, new acute ischemic symptoms. [2] They found isolated symptomatic intracranial stenosis >50% in 6.5% of patients, proximal middle cerebral artery occlusion in 3.7% and basilar artery occlusion in 1.2%. Mortality rates at 100 days for these 3 groups were dismal at 10.1%, 21.4%, and 44.7%, respectively. There was a higher rate of intracranial disease in African-American, Japanese, Chinese, and Hispanic patients, [3, 4] and conversely higher rates of extracranial disease in Caucasians. [5, 6]

In the US annually, there are approximately 750,000 strokes and an additional 250,000 TIAs. Extrapolation of these prevalence rates to the multi-cultural population of Rhode Island, leads to an estimated 200 to 300 strokes and TIAs every year from symptomatic intracranial atherosclerosis.

Natural History and Stroke Rates

Subsequent stroke rates in patients with symptomatic intracranial stenosis are high, especially in patients with >70% stenosis. Initial reports from medical subgroups in trials in the 1980s had suggested annual stroke rates of 7-8%, [7] but these trials suffered from poor follow-up and selection bias. There is a general paucity of natural history data among symptomatic, untreated patients. Among the more recent studies, Wong et et al. reported follow-up in 705 patients presenting with acute stroke.[8] One-year stroke rates for patients with intracranial atherosclerosis only and for patients with intracranial and extracranial atherosclerosis were 17.1% and 24.3%, despite medical therapy. In another series, 47 patients with >50% stenosis were evaluated and 38 patients completed 6 months of follow-up.[9] Thirteen patients (38%) suffered a stroke at 6 months. Medical therapy over this time was not reported.

The **GESICA (Groupe d'Etude des Stenoses Inta-Cranieenes Atheromateuses symptomatiques)** study prospectively evaluated symptomatic ICAD in 122 patients with a single stenosis of at least 50%. [10] During a mean follow-up period of 23.4 months, 38.2% of patients had a cerebrovascular event in the territory at risk, including stroke in 13.7% and TIA in 24.5%, despite antiplatelet or antithrombotic therapy.

Imaging

Four imaging modalities can be used to diagnose and characterize ICAD: conventional angiography, **Magnetic resonance angiography (MRA), Computed tomography angiography (CTA),** and **transcranial Doppler (TCD).** The latter 3 modalities are non-invasive while conventional angiography is minimally invasive.

Advantages of MRA are that the brain parenchyma can be characterized at the time of the exam and that no radiation or intravenous contrast is required (vessel imaging employs flow physics alone). Although CTA requires contrast and radiation, the spatial resolution is improved over MRA.

The purported advantages of TCD imaging is that it is non-invasive, a bedside examination, and less expensive. However, it is highly dependent on the experience of the operator and not all patients have acoustic windows.

The **Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA)** trial compared TCD and MRA with conventional angiography for the detection of >50% stenosis.[11] TCD and MRA had negative predictive values of 86% and 91%, respectively. Positive predictive values were less impressive (possibly due to low disease prevalence) at 36% and 59%, respectively.

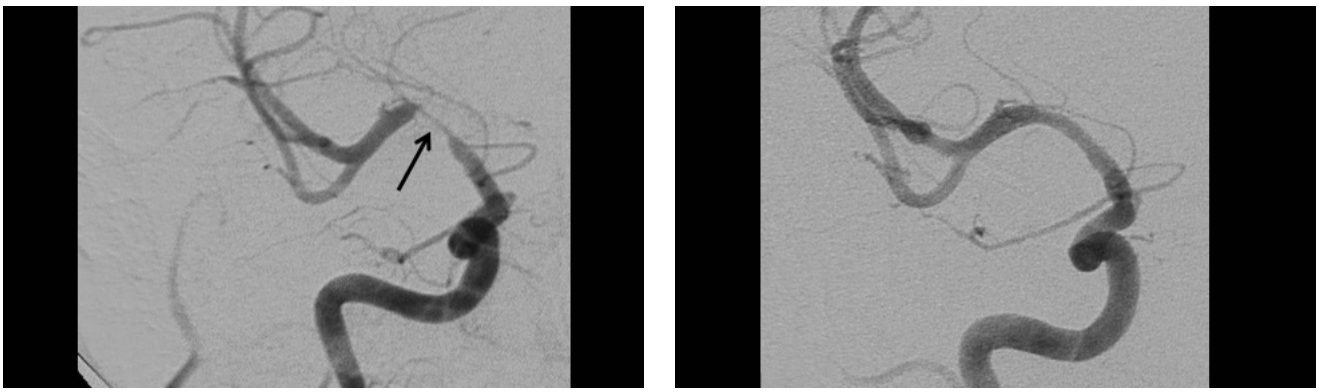

Figure 1. Images from intracranial angioplasty and stent placement in a 49 year old male who presented with crescendo TIAs in the right hemisphere, occurring despite antiplatelet agents. Initial angiogram shows a high grade stenosis of the right middle cerebral artery (MCA) (arrows, left). After angioplasty and stent placement, the vessel caliber is markedly improved and flow through this segment is greatly increased (right). The stent was placed in this case because of elastic recoil that occurred after the angioplasty (not shown).

Given the reasonably high negative predictive values of MRA and TCD, they can be used as initial imaging in patients. However, an abnormal MRA or TCD requires a confirmatory test. CTA is the best non-invasive test for intracranial atherosclerosis given its superior spatial resolution over MRA. Catheter angiography remains the best test for diagnostic purposes (Figure 1) because of its ability to accurately quantify the degree of stenosis and assess vessel morphology, but is usually reserved for patients who are considered for treatment with endovascular therapy.

Medical Therapy

The prospective, randomized **Warfarin-Aspirin Symptomatic Intracranial Disease (WASID)** trial showed that warfarin was of no benefit over aspirin in preventing recurrent stroke, and patients on warfarin had significantly higher rates of hemorrhage.[12] WASID was a multicenter, double-blinded trial of patients with symptomatic ICAD and lesions with >50% narrowing. Patients were randomized to ASA or warfarin, with primary endpoints being ischemic stroke, brain hemorrhage, and death from vascular causes. Although criticized for its non-standard ASA regimen and high rate of dropout for both medications (28.4% in warfarin group), the study was terminated prematurely as there were significantly higher rates of hemorrhage in warfarin group and warfarin provided no benefit over aspirin for the prevention of stroke. The primary endpoints were reached in 21% of patients at 2 years in the aspirin group and 22% of the warfarin group.

Subgroup analysis of the WASID data [2] pinpointed certain high risk subgroups: patients with severe stenoses (>70%), and those enrolled less than 17 days after the initial event. Patients with a >70% stenosis had a 23% chance of stroke at 1 year and 25% at 2 years, despite medical therapy. Even more sobering than the likelihood of stroke in patients with ICAD are the clinical consequences. Of the 106 strokes which occurred in the WASID study group, 73% were within the same territory as the stenotic lesion and 44% were disabling.

Cilostazol is the only other anti-platelet agent to be studied specifically in patients with symptomatic ICAD. Although no strokes were seen in either treatment group (cilostazol and aspirin vs. placebo and aspirin at 6 months, progression of ICAD as measured by MRA was less common in the cilostazol group (6.7% versus 28.8%; p=0.008). The TOSS-II trial is now ongoing and compares cilostazol and aspirin vs. clopidogrel and aspirin in patients with symptomatic ICAD.

Certainly optimal medical therapy for ICAD would include aggressive management of hypertension, smoking cessation, control of diabetes and hyperlipidemia. While no trials have directly compared more potent anti-platelet agents such as Clopidogrel (Plavix) or Asprin/Dipyridamole (Aggrenox), both of those agents are commonly used in ICAD patients.

Endovascular Therapy

Angioplasty

Given the dismal natural history of intracranial stenosis despite medical therapy, there has been great interest in using endovascular techniques to improve stroke-free survival. In 1980, Thoralf Sundt reported the first successful intracranial angioplasty. Early investigators reported highly disparate and, in some cases, dismal results. Among the first studies specifically looking at ICAD patients was the study by Higashida et al, showing a 38% major complication rate in treatment of 8 patients with symptoms refractory to medical management.[13] However, over the ensuing decade, significant technical refinements have resulted in a marked reduction in procedural complications.

Connors et al introduced the concept of "sub-maximal" angioplasty.[14] They showed that technical factors affected outcome. By using a balloon smaller than the native vessel (which differs from coronary and peripheral angioplasty where the balloon chosen is *the same size or larger* than the target vessel), and inflating slowly, the trauma to the vessel wall was markedly reduced, and with it, the procedural complication rate dropped substantially. Several recent groups have reported their results, and 30-day major complication rates have been reduced to between 4 and 6%. (Table 1)

While procedural success is key, the ultimate goal is prevention of further stroke. Many of the same groups have followed patients for a long term and have shown impressively low stroke rates. (Table 2) Clark documented no subsequent neurological events in 17 treated patients who were followed for a mean of 22 months.[15] Yoon reported similarly impressive results: only 1 TIA event in 32 patients followed for 20 months.[16] In their series of 120 patients with a mean follow-up of 42 months, Marks et al. reported a 3.2% stroke rate in the territory of treatment which included perioprocedural strokes and deaths.[17] Finally, Wojak reported an annual stroke rate of 1.8% in 60 patients with a mean follow-up of 45 months.[18] Considering that most of the patients in these series had >70% stenosis, these rates appear to be substantially lower than the natural history on medical therapy.

These same groups[17, 18] also provide data on restenosis in these patients. Symptomatic and angiographic restenosis occurred in approximately 5-10% and 10-30%, respectively, with a mean time to restenosis of 6 months.

All of these studies combine to show that intracranial angioplasty has matured to be a treatment that is safe, durable and effective at preventing recurrent stroke. What is lacking is randomized data comparing angioplasty with medical management alone, or with stenting.

Stenting

Many centers have taken a leap of faith and extrapolated data from coronary and peripheral artery disease, choosing to perform stent placement in addition to angioplasty. However, no data show a superiority of in-

Table 1

Series	N	Complication rate	Technical Success
Higashida et al. 1993	8	38%	
Clark et al. 1995	17	9.1%	
Marks et al. 1999	23	4.3%	
Connors et al. 1999	50	6.0%	98%
Yoon et al. 2005	32	6%	91%
Marks et al. 2006	120	5.8%	93%
Wojak et al. 2006	60	4.8%	91%

Table 2

Series	N	Mean Follow-up	Annual Stroke Rate
Clark et al. 1996	17	22	0%
Yoon et al. 2005	32	20	0%
Marks et al. 2006	120	42	3.2%
Wojak et al. 2006	60	45	1.8%

Table 3: Complication rates of intracranial stent placement for ICAD using balloon mounted stents.

Series	(n)	Complication Rate	Technical success
Gomez et al. 2000	12	5.3%	
Levy et al. 2001	11	36%	100%
SSYLIA 2004	43	6.6%	90%
Yu et al. 2005	18	16.7%	
Lylyk et al. 2005	104	9.5%	98%
Mazighi et al. 2006	28	14.2%	
Jiang et al. 2007	213	4.3%	92%

tracranial stenting over angioplasty alone in most patients with ICAD.

One of the early studies evaluating dedicated intracranial stent, the **Stenting of Symptomatic atherosclerotic Lesions in the Vertebral or Intracranial Arteries (SSYLVIA)** trial[19] was a nonrandomized phase I study to evaluate the frequency of subsequent stroke in ICAD patients with >50% stenosis. Although successful stent deployment was seen in 95%, the frequency of stroke at 30 days and 1 yr was 7.2% and 10.9% - which do not appear to be substantially different from the WASID natural history data.[12] Several other studies evaluated the use of balloon mounted stents for ICAD patients (Table 3), with most of these demonstrating higher complication rates than those of angioplasty alone.[10, 19-24]

Combining the lessons learned from submaximal angioplasty with the enhanced navigability of a self-expanding stent design, the Wingspan stent (Boston Scientific, Natick, MA) was introduced with the intent of being placed after angioplasty, to reduce restenosis and improve stroke free survival. A phase I study reported a 30-day death and ipsilateral stroke rate of 4.5%, confirming safety, with a 1-year stroke rate of 9.3%.[23] One concern about the Wingspan stent, however, is what appears to be a higher than expected restenosis rate. Despite this, the Winsgpan stent is helpful in the management of flow limiting dissections occurring during angioplasty, elastic recoil, or some patients with recurrent stenoses. Further data will be needed to determine if stenting offers any advantage over simple angioplasty alone in ICAD patients.

Future Directions

Perhaps the biggest area of interest in ICAD therapy is the recently started, NIH-funded, randomized study comparing maximal medical management alone with medical therapy and stent placement, the **Stenting vs. Aggressive Medical Management for Preventing Recurrent stroke in Intracranial Stenosis (SAMMPRIS)** trial (http://clinicaltrials.gov/ct2/show/NCT00576693). The goal is to enroll 640 patients, with the medical treatment group being monitored for blood pressure targets, cholesterol levels and anti-platelet therapy. Patients in the endovascular treatment arm will all be treated with Wingspan stent placement, in addition to maximal medical therapy. All patients will have greater than 70% stenosis of the target artery and have strokes or TIAs referable to that lesion. We eagerly await the results of this landmark trial.

Summary

Intracranial atherosclerosis accounts for 5 to 10% of all strokes. The natural history is poor, especially among patients with a greater than 70% stenosis. Studies of medical therapy have shown no benefit to warfarin over aspirin in these patients. In fact, patients with a greater than 70% stenosis who present with a stroke in the territory at risk have a 25% risk of stroke in the subsequent 24 months, despite medical therapy. First line therapy for these patients is aggressive risk factor management, including smoking cessation, blood pressure control, management of diabetes and correction of dyslipidemia. Intracranial angioplasty has a low complication rate between 4-6%, and low post-treatment annual stroke rate between 2-4%. What was once considered a very high risk procedure has now shown to be as safe as carotid endarterectomy for symptomatic patients. Stent placement can be performed in select cases as an adjunct to primary angioplasty. While we await the results of the SAMMPRIS trial, we can still offer aggressive medical and endovascular options for patients with this lethal disease.

From a management standpoint, we believe that intracranial imaging (TCD, MRA or CTA) should be performed in patients with stroke or TIA. Consultation with a neurologist would be helpful, as would consultation with a neurointerventional radiologist to help identify patients who may benefit from more aggressive endovascular therapy in conjunction with medical therapy.

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