The natural history of intracranial carotid artery atherosclerosis

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Intracranial atherosclerosis is the cause of a significant number of strokes. Despite maximal medical therapy, this disease continues to carry a poor prognosis. The authors reviewed studies in which the outcomes after conservative management in patients with intracranial carotid artery atherosclerosis were reported. Analysis of the literature demonstrates that maximal medical therapy frequently fails with this disease, leaving patients at high risk for cerebral infarction and death. A better understanding of the pathophysiological aspects and natural history of this condition may serve to guide clinical decision making and the choice of therapeutic options in this patient population.

KEY WORDS • carotid artery • intracranial atherosclerosis • natural history • stenosis

Cerebrovascular disease is the most common life-threatening neurological event in the US.² Intracranial atherosclerosis is responsible for approximately 40,000 of these events per year, representing 10% of all ischemic strokes.¹¹ In general, intracranial atherosclerosis is associated with several risk factors, many of which are the same as those for coronary artery disease. These include non-caucasian race, diabetes, hypertension, hypercholesterolemia, and cigarette smoking.^{11,12,15} Unfortunately, there are currently few treatment options for intracranial atherosclerosis, and despite maximal medical therapy, the prognosis for patients with this condition remains poor.

Endovascular procedures, which have recently gained popularity in the treatment of intracranial atherosclerosis, have tremendous potential to alter the current standard of care for cerebrovascular disease. These techniques, however, carry substantial risks, and their benefit must be weighed against the prognosis for conservative management in this patient population. In this paper we critically review relevant studies of medically managed intracranial CA atherosclerosis in an attempt to understand better the pathophysiological features and natural history of this condition.

Pathophysiological Features of Intracranial Atherosclerosis

The CA is the most frequent site of intracranial stenosis, accounting for approximately 50% of cases.¹ The overwhelming majority of these are diagnosed when the patient presents with an acute ischemic event, either

stroke or a TIA. Published data in studies in which transcranial Doppler ultrasonography and/or cerebral angiography were used have shown intracranial stenoses to be dynamic lesions that may undergo progression, regression, or remain stable during the follow-up period with medical treatment alone. The factors associated with atherosclerotic progression, however, have yet to be elucidated. In addition, current imaging modalities do not accurately predict the natural history of these lesions, leaving clinicians with difficult management decisions.

Our understanding of the pathological features of atherosclerotic plaque is based largely on autopsy studies. From these investigations, it appears that plaque morphology may be important in the setting of acute cerebrovascular syndromes. Two types of plaques exist; these are white and yellow. White plaques may be viewed as stable lesions with thick fibrous caps and low distensibility. In contrast, yellow plaques may be viewed as unstable, with thin fibrous caps, a lipid-rich core, and high distensibility. In comparison with white plaques, yellow plaques are more commonly found in the setting of acute coronary syndromes, indicating that yellow plaques have a higher level of mechanical vulnerability. Yellow plaques, however, become white plaques over time, potentially representing a healing process. Unfortunately, in vivo morphological data are still lacking because of limitations in angioscopic and ultrasonic technology.

Intracranial atherosclerosis may lead to stroke by three mechanisms: 1) perfusion failure; 2) local thrombosis with arterioarterial thromboembolism; and 3) occlusion of penetrating arteries. Each of these mechanisms results in different pathophysiological features with relevance to endovascular treatment. Perfusion failure occurs when the

Abbreviations used in this paper: CA = carotid artery; ICA = internal CA; TIA = transient ischemic attack.

collateral circulation is unable to compensate for a severe stenosis, leading to a reduction in distal blood flow. In this scenario, autoregulation allows reflex vasodilation to occur, thereby maintaining cerebral blood flow. Furthermore, the brain parenchyma is able to increase oxygen extraction in an attempt to maintain normal cerebral metabolism. Once these two compensatory pathways reach their limit, however, further decrement in perfusion leads to stroke. Patients with perfusion failure due to intracranial atherosclerosis may represent a subgroup of individuals for whom endovascular therapy has the greatest chance of being effective.

The second mechanism by which intracranial atherosclerosis may cause stroke is local thrombus formation associated with a preexisting atherosclerotic plaque. In this scenario, thrombosis may not only substantially occlude the parent vessel, but it may also result in arterioarterial embolization. These patients' disease can be effectively managed with antithrombotic treatment, statin medications, and angiotensin-converting enzyme antagonists to prevent local thrombosis and promote plaque stabilization.

The third mechanism by which intracranial atherosclerosis may cause stroke is occlusion of the origin of small arteries. Perforating arteries at risk include the lenticulostriate vessels off the middle cerebral arteries, thalamogeniculate vessels off the posterior cerebral arteries, and the median perforating and circumferential arteries off the basilar artery. Occlusion of these small vessels results in stroke in the deep structures within the cerebral hemispheres or brainstem. Therefore, atherosclerotic stenosis of large intracranial arteries may be associated with infarction of cerebral territories supplied by their perforating vessels. Such patients need to be thoroughly examined because endovascular therapy involving angioplasty may completely obstruct bordering arteries and lead to adverse outcomes.

Medical Management

Intracranial atherosclerosis is medically managed in a fashion analogous to that of systemic atherosclerosis, with the control of risk factors, use of antithrombotic medications, statins, and angiotensin-converting enzyme inhibitors. Endovascular therapy is considered only after maximal medical regimens have failed and patients have suffered recurrent TIA or strokes. Maximal medical regimens involve therapeutic doses of aspirin, ticlopidine, clopidogrel, warfarin, or intravenous heparin.^{7,13} Patients who continue to be symptomatic while receiving antiplatelet medications are frequently switched to anticoagulant drugs. The efficacy of aspirin compared with warfarin, however, is still controversial, with previous investigations demonstrating conflicting results.^{7,10,13}

Recently, a prospective randomized trial that sought to clarify this controversy, the Warfarin–Aspirin Symptomatic Intracranial Diseases Trial, was prematurely halted by the Safety Monitoring Committee after warfarin was associated with a higher incidence of hemorrhage. At the time of the trial's termination, 569 patients had been studied with a mean follow-up duration of 1.7 years, and no difference in efficacy was detected between the two treatments.^{5,6} Currently, another randomized trial specifically

addressing the issue of proper medical management of symptomatic intracranial atherosclerosis, the Aspirin Versus Anticoagulants in Symptomatic Intracranial Stenosis trial, is underway. We hope that the results of this study will clarify this topic and delineate the most efficacious management of the disease in this patient population.

Prognosis of Patients With Intracranial CA Atherosclerosis

In the largest retrospective series, Borozan, et al.,⁴ reviewed the outcomes in 93 patients with angiographically documented intracranial stenosis of at least 20%. Seventy-one patients had unilateral and 22 had bilateral disease; 24% were symptomatic. Over a mean follow-up period of 22.5 months, 23% of patients died; cardiac disease was the cause of death in six individuals (6.5%). The annual ipsilateral stroke and mortality rates were 5.1 and 10.3%, respectively. These individuals were identified among 885 consecutive patients in whom cerebral angiograms were obtained.

Marzewski, et al.,⁹ published the first detailed review regarding the outcomes in 66 patients with angiographically documented intracranial ICA stenosis of at least 50%; 41% of these patients were symptomatic. Over a mean follow-up duration of 3.9 years, 12.1% of patients experienced an isolated TIA in the ICA territory and 15% suffered a stroke. In this study, 50% of patients died during the follow-up period; cardiac disease was the cause of death in 18 individuals (27.2%). The ipsilateral stroke rate was 3.1% annually.

Another retrospective series was published by Craig, et al.⁸ These authors reviewed the outcomes in patients with angiographically documented intracranial stenosis of at least 30%. Of these 58 patients, 81% were symptomatic. After a mean follow-up duration of 30 months, the authors found that 43% of patients experienced an isolated TIA or stroke in the ICA territory. In addition, 43% of patients died during the follow-up period; cardiac disease was the cause of death in 11 individuals (19%). The annual ipsilateral stroke and mortality rates were 7.6 and 17.2%, respectively. Of interest, there were no differences between the death rates in symptomatic (42%) and asymptomatic (45%) patients.

Bogousslavsky³ reviewed the outcomes in 22 patients with angiographically documented intracranial stenosis of at least 30%. Over a mean follow-up period of 40.4 months, 32% of patients died; cardiac disease was the cause of death in six individuals (27.3%). The annual ipsilateral stroke and mortality rates were 8.1 and 9.5%, respectively.

Wechsler, et al.,¹⁴ reviewed the outcomes in 15 patients with angiographically documented intracranial stenosis of at least 50%; 80% of these patients were symptomatic. Over a mean follow-up period of 51 months, 20% of patients suffered a stroke in the ICA territory. In this study, 20% of patients died during the follow-up period; cardiac disease was the cause of death in two individuals (13.3%). The annual ipsilateral stroke and mortality rates were 3.1 and 4.7%, respectively. An important finding in this study was that the initial clinical presentation correlated with the presence of hemodynamically significant stenosis; 71% of symptomatic patients had evidence of impaired flow on

angiography. In comparison, only 20% of asymptomatic patients had similar findings. The authors hypothesized that the strokes were the result of embolism distal to the stenosis and that TIAs were the result of slow flow.

The aforementioned studies reveal annual mortality and ipsilateral stroke rates ranging from 4.7 to 17.2% and 3.1 to 7.6%, respectively. Nevertheless, these investigations have limitations that must be taken into account when interpreting their results. First, each is subject to retrospective bias due to the study design. Second, the patient populations are highly selective and variable, with availability of cerebral angiography studies as an entry criterion and degrees of stenosis ranging from 20 to 70%. Third, the cohorts are small and heterogeneous, and the severity of ipsilateral stroke is not clearly defined. Regardless of their limitations, however, these studies indicate that patients with intracranial CA atherosclerosis are at high risk for recurrent stroke or death and that medical management frequently fails in their treatment. Future prospective investigations are needed to clarify the prognosis for these patients.

CONCLUSIONS

Despite maximal medical management, intracranial CA atherosclerosis continues to portend a poor prognosis. Conservative management frequently fails in this disease, leaving patients at high risk for cerebral infarction and death. Given the natural history of this condition, advancements in its treatment, particularly those related to endovascular methods, are of the utmost importance.

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