Secondary Prevention of Atherothrombotic or Cryptogenic Stroke

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Case Presentation

A 65-year-old woman presents to the Emergency Department at 10:00 A.M. with abrupt onset of slurred speech and right arm weakness the previous night and no improvement today. She has a history of diabetes mellitus and hypertension. Magnetic resonance imaging (MRI) reveals a small acute ischemic lesion in the left basal ganglia.

Initial Evaluation

The diagnostic evaluation (Figure) after an acute ischemic stroke should be initiated urgently, because the highest risk period for recurrent stroke is the first few days after the initial event. Identification of the most likely cause as well as risk factors for recurrent ischemic events is the objective of this evaluation. An MRI[1] of the brain is the most sensitive imaging study to detect an acute ischemic stroke. An MR angiogram (MRA) of the cervical and intracranial vessels can be included to help identify relevant cerebrovascular lesions. If MRI is not available, a computed tomography (CT) combined with CT angiogram (or cervical ultrasound) can be used for initial diagnostic assessment. Based on the results of the initial neuroimaging studies, the stroke can be classified into preliminary diagnostic categories: large vessel occlusion, small vessel occlusion, potential cardioembolic, or unknown/other.[2] If there is no relevant large vessel lesion (such as an ipsilateral carotid stenosis) and the ischemic stroke does not appear to be lacunar (small maximal diameter and subcortical location), then additional evaluation to look for a cardioembolic source should be performed; diagnostic options include a 12-lead ECG, a transthoracic or transesophageal echo,[3] and longer term cardiac monitoring for paroxysmal atrial fibrillation. We will focus on prevention of recurrent stroke of atherothrombotic (noncardioembolic) origin.

Management of Risk Factors

Risk factor modification is a key component of secondary stroke prevention; therefore, evaluation for common vascular risk factors, including hypertension, dyslipidemia, and diabetes mellitus, is essential. In general, 3 therapeutic strategies are appropriate for virtually all patients with atherothrombotic stroke: an antiplatelet agent, antihypertensive therapy, and statin therapy.

Antiplatelet therapy is a cornerstone of secondary prevention of atherothrombotic stroke (Table 1). Therapeutic choices include aspirin, clopidogrel, or the combination of dipyridamole+aspirin (DYP+ASA). Aspirin, at doses of ≥50 mg per day, provide ≈15% to 20% relative risk reduction for secondary prevention of ischemic stroke. Low doses (75–100 mg) are generally recommended to reduce gastrointestinal toxicity.[2] The A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE) study demonstrated superior efficacy of clopidogrel over aspirin for prevention of vascular end points in patients with stroke and other vascular disorders.[2] Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT) and European Stroke Prevention Study 2: Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke (ESPS 2) demonstrated that DYP+ASA is superior to aspirin alone for prevention of recurrent vascular events in stroke patients. Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS)[2] directly compared clopidogrel versus DYP+ASA and demonstrated similar rates of recurrent stroke; the composite outcome of stroke, myocardial infarction, and all vascular death was identical.[2] Thus, there is no apparent

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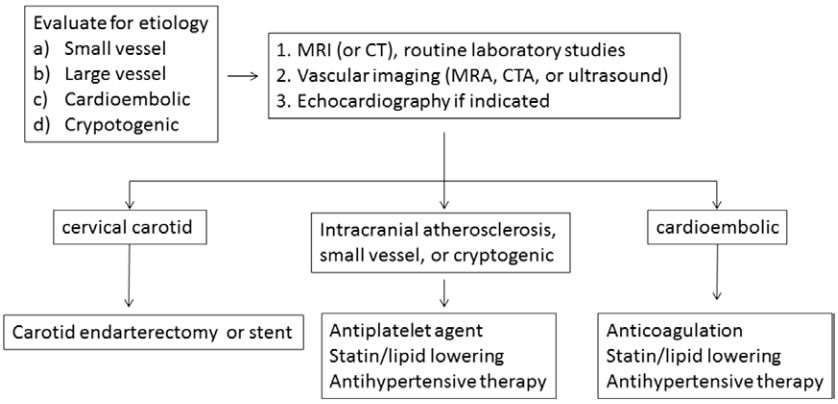

Figure. Diagnostic and therapeutic algorithm of atherothrombotic stroke. CT indicates computed tomography; CTA, CT angiogram; MRA, magnetic resonance angiogram; and MRI, MR imaging.

efficacy advantage of DYP+ASA versus clopidogrel for secondary stroke prevention. The combination of clopidogrel and aspirin is associated with a more frequent adverse effect profile (including a higher rate of intracerebral hemorrhage) than clopidogrel alone in subacute stroke patients and is generally not recommended. Most clinicians take economic factors, side effect profiles, and formulary options into consideration when choosing a specific antiplatelet agent for stroke prevention. Prasugrel (a newer thienopyridine inhibitor) appears to have an increased risk of intracranial hemorrhage in patients with history of stroke or transient ischemia attack. Therefore, this agent is not recommended for secondary stroke prevention.[6]

Because hypertension is the most prevalent risk factor for stroke, blood pressure management is vital for secondary stroke prevention. Lowering blood pressure regardless of initial blood pressure may be beneficial as long as adverse events related to hypotension do not occur.[7] The degree of blood pressure reduction achieved is more important than the specific class of antihypertensive chosen.[8]

Cholesterol reduction therapy is another mainstay of stroke prevention, and statin therapy is preferred. The SPARCL study demonstrated that high-dose atorvastatin (80 mg/d) is beneficial for secondary prevention of atherothrombotic stroke and has an acceptable adverse effect profile in ischemic stroke patients.[9] In Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL), patients who achieved the lowest low-density lipoprotein levels had the lowest stroke rates. Diabetes mellitus is another important stroke risk factor; we recommend a goal hemoglobin A1C <7.0% for secondary prevention.[2]

Lifestyle Modification

Several lifestyle factors affect risk for first and recurrent ischemic stroke (Table 2).[10] These include the following: physical inactivity, tobacco use, obesity, alcohol consumption, and drug abuse (last 2 being less documented risk factors).

Many papers have attributed tobacco smoke as a potent modifiable risk factor for both ischemic and hemorrhagic stroke. Hence, we strongly advise patients to enroll in a tobacco cessation program. A combination of pharmacological support, cognitive and behavioral training, and skills training has been shown effective in tobacco cessation.[10]

Physical inactivity has been associated with increased all-cause mortality, cardiovascular mortality, and stroke. As per the American Heart Association guidelines, we recommend 150 minutes of moderate cardiovascular exercise a week.[10] Prospective studies have shown association of increase in body mass index and increase in stroke mortality. Obesity has also been shown to be associated with hypertension. Thus, we recommend weight reduction as a means to both reduce hypertension, a major risk factor for stroke, and a means to reduce risk of stroke.[10]

Various dietary studies have identified low potassium intake, excess salt intake, excess weight, and excess alcohol as potential contributors to elevated blood pressure. Thus, recommendations to increase fruits and vegetables and to reduce excess salt seem reasonable.

High amounts of alcohol consumption are associated with increased risk of all stroke subtypes, whereas low levels of consumption (≤2 drinks/d for men, ≤1 drink/d for women) are associated with reduced risk of stroke.[10]

Addressing these lifestyle issues during the initial emergent evaluation and index hospitalization is advised.[10]

Table 1. Risk Reduction for Vascular Events With Antiplatelet Agents for Secondary Stroke Prevention

Antiplatelet	Mechanism of Action	Relative Risk Reduction
Aspirin	Inhibits the enzyme cyclooxygenase, reducing production of thromboxane A2, a stimulator of platelet aggregation	17% RRR compared with placebo[4]
Clopidogrel	Thienopyridine that inhibits ADP-dependent platelet aggregation	RRR=10% compared with aspirin[4]
Dipyrimodole (+aspirin)	Inhibiting the activity of adenosine deaminase and phosphodiesterase (+aspirin)	Same efficacy as clopidogrel[5]

RRR indicates relative risk reduction.

Secondary Prevention by Stroke Mechanism

Large vessel disease includes cervical carotid disease, extracranial vertebral disease, or intracranial large vessels, such as the middle, anterior, or posterior cerebral arteries or the basilar artery.

Table 2. Recommendations for Modifiable Lifestyle Factors*

Lifestyle Factor	Relative Risk	Recommendation
Physical inactivity	2.7	Moderate exercise 150 min a week
Tobacco use	1.9, 50% reduction by end of year one	Counseling, nicotine replacement therapy for cessation
Obesity	1.39 stroke death increase/5 BMI point increase	Moderate weight loss
Alcohol consumption	1.6	≤2 glasses a day for men, ≤1 glass a day for women
Drug abuse	2–4.95	Counseling and cessation

BMI indicates body mass index.
*Data from American Heart Association Guidelines for Primary Prevention of Stroke, 2011[10]

Cervical Carotid Disease

Patients with a small ipsilateral ischemic stroke or transient ischemic attack who have moderate to severe cervical internal carotid arterial disease (>50%) are typically referred for carotid endarterectomy.[2]

Several studies have evaluated the safety and efficacy of cervical carotid angioplasty and stenting as an alternative method of treating carotid stenosis. The Stenting versus Endarterectomy for Treatment of Carotid-Artery Stenosis (CREST) trial suggests that stenting is noninferior to carotid endarterectomy, whereas subgroup analyses indicated that patients aged >70 years had better outcomes with carotid endarterectomy.[11] In addition, patients in the stenting arm had more postprocedure strokes, whereas patients in the endarterectomy arm had more postprocedure myocardial infarctions.[11]

Intracranial Atherosclerosis

Several studies[2] have evaluated therapeutic options for patients with symptomatic intracranial atherosclerosis. Vitamin K antagonists have not demonstrated greater efficacy than antiplatelet agents for preventing recurrent stroke. More recently, Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) demonstrated that medical management with antiplatelet therapy, aggressive statin therapy, and blood pressure lowering is associated with better outcomes than intracranial stenting.[12] This trial documented a high periprocedure stroke risk after intracranial stenting.[12] The risks and benefit of intracranial angioplasty without stenting are not well established.

Small Vessel Disease (Lacunar Stroke)

The recent Secondary Prevention of Small Subcortical Strokes (SPS3)[13] trial demonstrated that for patients with lacunar strokes, long-term dual antiplatelet therapy with low-dose aspirin and clopidogrel is associated with less desirable outcomes than aspirin alone (higher hemorrhage rates and increased all-cause mortality).

Cryptogenic Stroke

Despite routine diagnostic evaluation, up to a third of all ischemic strokes remain cryptogenic.[14] A patient may first be described as having cryptogenic stroke after completing routine evaluation (Figure), but sometimes after further evaluation, such as extended cardiac monitoring, it may be discovered that the patient had paroxysmal atrial fibrillation as the cause, in which the diagnosis of the stroke would be changed to ischemic stroke of cardioembolic origin.

One of the most important and prevalent causes detected in patients initially suspected of cryptogenic stroke is paroxysmal atrial fibrillation (PAF). Traditional 2- to 3-day Holter monitoring may reveal subclinical atrial fibrillation in 6%.[15] A 30-day autotriggered monitoring study (Stroke and Monitoring for PAF in Real Time [SMART] Registry) revealed a PAF detection rate of 11%.[16] Several studies have shown that longer term (2–3 week) monitoring has a yield of about 20%.[15] The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)[17] trial found that among patients who had a pacemaker implanted, 10% had subclinical tachyarrhythmias by their 3-month visits. Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL AF) trial (NCT00924638) is another study investigating implanted recording for arrhythmia for up to 6 months; final results of this study are pending. Long-term monitoring for up to 3 years in the Stroke Prior to Diagnosis of Atrial Fibrillation Using Longterm Observation With Implantable Cardiac Monitoring Apparatus (SURPRISE) prospective observational study suggests higher detection rates of 17% (NCT01498146), whereas another recent cohort study evaluating implantable loop recorder had detection rate of 25% when monitoring patients for up to 51 days.[18] We routinely recommend extended cardiac monitoring in presumed cryptogenic stroke patients, ideally for at least 2 weeks, starting as soon as possible after the stroke. The diagnostic yield for detecting PAF is often highest soon after the stroke.[15] If PAF is documented, then oral anticoagulation is indicated. If after thorough evaluation the cause remains cryptogenic, we recommend antiplatelet therapy and aggressive risk factor reduction.[2]

Extensive testing for thrombophilia has a low yield, as only a small portion of ischemic arterial strokes are related to an inherited thrombophilia.[2] Although previously thought to play an important role, mitral valve prolapse does not appear to explain many cryptogenic strokes.

Patent foramen ovale (PFO) management remains controversial. Retrospective data have demonstrated an association between PFO with cryptogenic stroke. Prospective trials[19–21] document low recurrent stroke rates in cryptogenic stoke patients

with PFOs and did not find PFO closure to be effective for preventing recurrent stroke. Two recent, independently conducted studies using a different PFO closure device reported no significant benefit in the intention to treat analysis.[20,21] One of them (Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment [RESPECT] study) showed a statistically significant benefit when using a per-protocol analysis.[20] Both studies demonstrated modestly lower rates of ischemic stroke in the intervention arms, but because the risk of stroke recurrence was low in the medical therapy arm, no statistically significant difference could be observed with the intervention. We generally do not recommend PFO closure.[22] One randomized study (PFO in Cryptogenic Stroke Study [PICSS]) investigated warfarin versus aspirin for patients with confirmed PFO and found no significant difference in recurrent event rate.[23] Given the nontrivial bleeding risk for warfarin, we typically recommend antiplatelet therapy and risk factor reduction for patients with cryptogenic stroke and PFO.

Case Resolution

The patient in the above vignette appears to have a small vessel (lacunar) stroke. Our therapeutic recommendations are an antiplatelet agent (either clopidogrel 75 mg/d or aspirin 81 mg/d), atorvastatin (80 mg/d), and an antihypertensive agent to goal blood pressure ≤120/80 mm Hg. The patient should also be advised about lifestyle modification, including tobacco cessation, weight loss if indicated, and moderate cardiovascular exercise.

Disclosures

None.

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