Evaluation and Management of Ischemic Stroke

Lucy Lu

ABSTRACT
Stroke is the leading cause of disability and third leading cause of mortality in Canada. Ischemic strokes, which account for 80% of all strokes, result from embolism or thrombosis. Common etiologies of ischemic stroke include: atrial fibrillation, carotid artery stenosis, patent foramen ovale and hypercoagulable states. Timely recognition and management of ischemic stroke are crucial in reducing its associated morbidity and mortality. The purpose of this review is to discuss current guidelines pertaining to the evaluation, management and secondary prevention of ischemic stroke.

INTRODUCTION
Stroke is characterized by rapidly developing clinical signs of neurologic dysfunction caused by a sudden loss of perfusion to a cerebral vascular territory. The age-dependent incidence of stroke is 1-2 per 1,000 population, affecting 50,000 Canadians each year. It is the leading cause of adult disability in Canada, and the third leading cause of death, costing the Canadian economy $4 billion annually.

Stroke is classified as ischemic or hemorrhagic. Intracranial hemorrhage accounts for 10% to 15% of all strokes. The rest are ischemic, caused by a disruption of blood flow, glucose, or oxygen to the brain. The brain is the most metabolically active organ in the body, so it is extremely sensitive to decreased blood flow; an ischemic cascade begins seconds to minutes after onset of ischemia and is characterized by neuronal injury and death. Core brain tissue receiving less than 20% of blood flow suffers irreversible infarction within minutes. The ischemic penumbra, which surrounds the core tissue, may remain viable for a few hours due to collateral supply of blood. As a result, early recognition and management of stroke is crucial to preserving the penumbral neurons and reducing stroke severity. This paper will delve into common mechanisms of ischemic stroke and focus on current guidelines for its evaluation and management.

METHODS
A literature search was performed using the PubMed database with combinations of keywords: “ischemic stroke”, “etiology”, “risk factor”, “acute management”, “secondary prevention”, “review” and “guidelines”. Reference lists of the articles identified were used to find additional manuscripts that were judged to be relevant.

ETIOLOGY
Ischemic strokes may be caused by embolism, thrombosis, or hypoperfusion. Twenty-five percent of ischemic strokes are embolic, occurring when a cerebral artery is blocked by a clot or other debris from a distant site in the body. Embolic strokes may simultaneously cause multiple infarcts in different cerebral vascular territories. Emboli can originate from the heart, arteries or veins and often occur in hypercoagulable states, such as in antiphospholipid syndrome, protein C and protein S deficiencies. Cardiogenic emboli may arise in conditions predisposing to blood stasis, such as atrial fibrillation, recent myocardial infarction (MI), dilated cardiomyopathy and severe congestive heart failure (CHF). Thrombi may also develop on valves that are diseased, damaged or prosthetic. Atherothrombolic or cholesterol emboli may originate in the aortic arch or extracranial arteries, including the carotid and vertebral arteries. Paradoxical emboli, arising in the venous circulation, can pass into the arterial system through a cardiac septal defect, such as a patent foramen ovale (PFO), and travel to the brain.

Thrombotic strokes, accounting for 50% of ischemic strokes, are caused by the formation of thrombi that occlude cerebral arteries (Figure 1). Large-vessel thrombosis involves the carotid and vertebral arteries and the Circle of
Willis. Obstruction of these vessels is usually due to rupture of atherosclerotic plaque, although, in younger patients, the differential diagnosis includes arterial dissection, fibromuscular dysplasia, vasculitis, sickle cell anemia, polycythemia, vasoconstriction from migraine or substance abuse and other hypercoagulable states. Small-vessel thrombotic strokes, also known as lacunar strokes, involve small, deep penetrating cerebral arteries. Occlusions of the smaller arteries are commonly the results of microatheroma (small atherosclerotic plaque) and lipohyalinosis (fatty hyaline buildup). Cerebral venous thrombosis is a rare cause of stroke, occurring when venous sinuses drainage of cerebral blood flow is blocked; cerebral infarction is secondary to tissue congestion and inadequate arterial perfusion pressure.

The causes and mechanisms of ischemic stroke are summarized in Figure 2.

**RISK FACTORS**

The most important risk factor for stroke is age, with risk of stroke doubling every decade. Other risk factors include: hypertension, atrial fibrillation, CHF, hyperlipidemia, diabetes, recent coronary artery bypass surgery, obesity, smoking and heavy alcohol consumption.

Cardiogenic strokes, caused by atrial fibrillation, are associated with higher mortality, more severe disability and more frequent recurrence. The CHADS2 score can be used to quantify stroke risk in a patient with atrial fibrillation. One point is scored for each of the following conditions: Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, and two points are added if there is a history of Stroke or transient ischemic attacks. A CHADS2 score of zero or one signifies a low risk of stroke, whereas a CHADS2 score of two or more implies the annual risk of stroke is greater than 4% and anticoagulation therapy is warranted.

Transient ischemic attacks (TIA) can be warning signs for a future ischemic event. TIAs present with stroke-like symptoms that resolve in minutes to hours. They differ from ischemic strokes in that the neurologic dysfunction is temporary, resulting from focal cerebral ischemia without acute infarction. The ABCD2 score system is used to predict stroke risk after TIA (Table 1). Since the mechanism causing cerebral ischemia in a TIA may progress to an ischemic stroke, TIAs should be investigated within 48 hours, especially for high-risk patients (ABCD2 score ≥4).

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**Figure 1.** Cerebral Vascular Anatomy. Images reproduced from The Merck Manual Medical Library, http://www.merckmanuals.com/professional/

Less commonly, systemic hypoperfusion, from decreased cardiac output or hypovolemia, may lead to decreased cerebral blood flow and cause watershed infarcts. Vascular border zones between two cerebral arteries, called watershed areas, have the lowest perfusion pressures and are therefore most prone to damage.
Table 1. ABCD2 Score

<table>
<thead>
<tr>
<th>Feature</th>
<th>Points</th>
</tr>
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<tbody>
<tr>
<td>Age ≥60 years</td>
<td>1</td>
</tr>
<tr>
<td>Blood pressure (BP) elevation:</td>
<td>1</td>
</tr>
<tr>
<td>Systolic BP ≥140 mmHg or Diastolic BP ≥90 mmHg</td>
<td></td>
</tr>
<tr>
<td>Clinical features:</td>
<td></td>
</tr>
<tr>
<td>Unilateral weakness</td>
<td>2</td>
</tr>
<tr>
<td>Speech impairment without focal weakness</td>
<td>1</td>
</tr>
<tr>
<td>Duration of TIA:</td>
<td></td>
</tr>
<tr>
<td>≥60 mins</td>
<td>2</td>
</tr>
<tr>
<td>10-59 mins</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
</tbody>
</table>

Risk of Stroke after a TIA

<table>
<thead>
<tr>
<th>ABCD2 Score</th>
<th>2-day risk</th>
<th>7-day risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-3</td>
<td>1%</td>
<td>1.2%</td>
</tr>
<tr>
<td>4-5</td>
<td>4.1%</td>
<td>5.9%</td>
</tr>
<tr>
<td>6-7</td>
<td>8.1%</td>
<td>12%</td>
</tr>
</tbody>
</table>

PRIMARY EVALUATION

Since stroke is a medical emergency, it is important to establish the patient’s airway, breathing and circulation and draw the relevant bloodwork prior to proceeding with a focused history and physical exam. On history it is important to note any risk factors for stroke and determine the time of onset of symptoms in order to assess the patient’s suitability for thrombolytic therapy. Rarer causes of stroke should be considered in younger patients, including recent trauma, coagulopathies, migraine, oral contraceptive use and illicit drug use. Witnesses and family members may provide helpful information and help establish the patient’s baseline condition.

Most stroke presentations include unilateral numbness or weakness of the face, arm or leg, difficulty speaking or understanding, visual disturbances, dizziness and loss of balance. Symptoms are typically maximal at onset and do not progress. Deficits that worsen or fluctuate over time, may suggest a propagating thrombus, recurrent emboli, edema expansion, vasculitis or hypoperfusion.

Stroke must be distinguished from other disorders that may present similarly, including seizure, hypoglycemia, tumor, infection, hyponatremia, migraine, multiple sclerosis and intracranial hematoma. The likelihood of stroke increases with presence of any of these three findings: acute facial paresis, arm drift or speech disturbance.

It is important to closely monitor vital signs, since a stroke patient’s condition may rapidly deteriorate. The National Institute of Health (NIH) Stroke Scale is a validated tool for quantifying stroke severity and assessing clinical progression of deficits. It measures neurological function including level of consciousness, vision, extraocular movements, facial palsy, speech, language, ataxia, negate and motor and sensory deficits. The numerical score, calculated from the functional impairments elicited on physical exam, is a good predictor of outcomes: a score of 16 or greater predicts a high probability of death or severe disability, while a score of six or less forecasts a good recovery.

An emergent non-contrast head CT is required to differentiate ischemic stroke from hemorrhagic stroke and other neuropathologies, such as tumor and abscess. The earliest sign seen on CT is the loss of grey-white matter differentiation, caused by edema in the grey matter. While the CT scan may

Table 2. Common Symptoms and Signs of Specific Stroke Syndromes


<table>
<thead>
<tr>
<th>Anterior Cerebral Stroke</th>
<th>Middle Cerebral Stroke</th>
<th>Posterior Cerebral Stroke</th>
<th>Vertebrabasilar Stroke</th>
<th>Lacunar Stroke</th>
</tr>
</thead>
</table>
indicate the anatomic distribution and extent of the ischemia, clinical correlation is important in determining the specific stroke syndrome (Table 2). When a major cerebral artery is occluded by a thrombus, it may appear hyperdense on CT indicating that its arterial territory is at risk of infarction. The CT may appear normal initially, if there has not been sufficient edema buildup in the first six hours after the stroke. Diffusion-weighted magnetic resonance imaging (MRI) may be more sensitive at picking up acute ischemia, but the longer study duration and lack of availability make it unsuitable for the acute stroke setting. The rest of the primary assessment should be guided by the clinical scenario and may include auscultation for carotid bruits and heart murmurs, fundoscopy to look for signs of peripheral emboli, and bilateral blood pressures to rule out aortic dissection.

**ACUTE MANAGEMENT**

The primary goal of management in acute ischemic stroke is to minimize damage. If no hemorrhage is identified on the head CT, intravenous recombinant tissue plaminogen activator (IV rtPA) may be beneficial if administered within three hours of ischemic stroke onset. Its inclusion and exclusion criteria are outlined in Table 3. For certain patients meeting additional exclusion criteria (age >80, history of diabetes or stroke, patients on oral anticoagulation, or NIH stroke score >25), rtPA may be administered within 4.5 hours. Blood pressure must be maintained below 185/110 mmHg in tPA candidates, and no anticoagulants or antiplatelet agents may be administered within 24 hours of tPA administration.

Potential risks and benefits of rtPA should be discussed with patients and family members. The National Institute of Neurological Disorders and Stroke (NINDS) tPA trial showed that despite the 10-fold greater risk of intracerebral hemorrhage (6.4% with tPA vs. 0.6% in patients with traditional treatment), tPA produced a 12% absolute increase in excellent functional outcome and a 4% absolute risk reduction in mortality.

For patients who are not candidates for IV rtPA, intra-arterial (IA) tPA may be considered if they are presenting within six hours of stroke onset and have a large vessel occlusion identified on a CT angiography (CTA). For patients who are not qualified for tPA, aspirin (325 mg/day) administered within 48 hours post ischemic stroke can reduce risks of early mortality, disability and stroke recurrence.

High blood pressure is required to perfuse ischemic brain tissues, and should not be lowered unless it exceeds 220/120 mmHg, there is evidence of MI, CHF or aortic dissection, or thrombolytic therapy is planned. Hydration with isotonic maintenance fluids is important. Hyperglycemia, hypomagnesemia and fever worsen outcome and should be avoided. Nonambulatory patients should receive subcutaneous enoxaparin for deep venous thrombosis prophylaxis. In the days following the initial stroke, patients should be monitored closely for complications, including increased intracerebral pressure, seizures, depression, infection, pulmonary embolism and cardiac problems.
a TIA or stroke in the ipsilateral side. If symptomatic carotid stenosis is found, the diagnosis and degree of stenosis need to be confirmed by CTA, especially in the preoperative evaluation for carotid endarterectomy.

In addition, CTA can help depict detailed cerebrovascular anatomy and demonstrate subtle vascular occlusions from fibromuscular dysplasia, vasculitis and arterial dissection.

If cardiac causes of ischemic stroke are suspected, patients should be put on a Holter monitor to detect paroxysmal atrial fibrillation. An echocardiogram with bubble study can be obtained to identify presence of a patent foramen ovale, cardiac thrombi and valvular vegetations. In patients less than 40 years of age, a workup for hypercoagulability disorders and autoimmune diseases should be conducted. These patients should be investigated for antiphospholipid syndrome, protein C and S deficiencies, Factor V Leiden thrombophilia, lupus, sickle cell anemia, hyperhomocysteinemia and heparin-induced thrombocytopenia. Rhematologic markers, including erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody and antineutrophilic cytoplasmic antibody, should be tested.

SECONDARY PREVENTION

After an initial stroke, the risk of recurrence is at least 5% per year. Secondary prevention should begin immediately and should be tailored toward the underlying etiology. Warfarin reduces recurrent stroke risk by 64% in patients with atrial fibrillation, though it is associated with increased risk of bleeding. A combination therapy of clopidogrel plus aspirin may be considered for patients who cannot take warfarin.

Patients with symptomatic high-grade carotid stenosis (>70% stenosis) should undergo carotid endarterectomy within two weeks of the stroke, while patients with symptomatic carotid stenosis (50-60% stenosis) should have endarterectomy within one month. Stenting may be considered if endarterectomy is contraindicated or if there is bilateral symptomatic high-grade stenosis. Surgical intervention is not indicated in asymptomatic carotid stenosis as the operative risk exceeds the benefit. With or without surgery, all patients with carotid stenosis should be managed medically with a statin, antihypertensives and antiplatelet agents.

Strokes from other etiologies are generally managed with antiplatelet therapy. Aspirin (50 mg or 325 mg per day) is the initial choice because of its low cost, low risk and a 22% risk reduction in recurrent stroke. Studies have shown that Aggrenox (aspirin plus extended-release dipyridamole) may be superior to aspirin alone, with a 37% risk reduction, and can be considered as an alternative first-line therapy. Clopidogrel is recommended if there is an aspirin allergy or if aspirin therapy fails. The combination of clopidogrel and aspirin is not indicated due to increased bleeding risk without added benefit. Ticlopidine is a third-line therapy because of cost and the serious side effect of neutropenia. Long-term blood pressure control is important in secondary prevention of stroke. Blood pressure should be maintained below 140/90 mmHg in patients who suffered a stroke, and below 130/80 mmHg in stroke patients with diabetes and chronic renal disease. Additionally, an angiotensin-converting enzyme (ACE) inhibitor combined with a diuretic have been shown to reduce recurrent stroke risk by 43% in both hypertensive and nonhypertensive individuals. Thus this combination therapy should be initiated in all ischemic stroke patients prior to discharge from hospital or within the first week after the stroke regardless of their baseline blood pressure. Benefits start to appear with a reduction of 10/5 mmHg in blood pressure.

Atorvastatin 80 mg has been shown in a large randomized controlled trial to reduce the risk of stroke by 16%. All patients with prior ischemic strokes should be treated with statins irrespective of their cholesterol level because of reduction of both fatal and non-fatal stroke.

CONCLUSION

As a leading cause of morbidity and mortality in Canada, timely recognition and management of stroke is imperative. Ischemic strokes, which account for 80% of all strokes, typically result from one of three mechanisms: embolism, thrombosis and hypoperfusion. There are a variety of etiologies, the determination of which is essential in targeting therapy and guiding secondary prevention. In acute stroke management, a focused history and physical exam should be completed within 10 to 15 minutes of the patient’s arrival in the emergency department to obtain information about the time of onset, symptoms, course, stroke risk factors, past medical history, neurologic deficits and cardiac function. An emergent CT head should be performed to distinguish ischemic stroke from hemorrhagic stroke and treatment with IV rtPA, IA rtPA or aspirin may be considered depending on the timing and patient suitability.

Research in ischemic stroke management is ongoing, new therapies are emerging, and clinical guidelines are constantly optimized for better patient care. For instance, dabigatran, a direct thrombin inhibitor, has recently been approved as an alternative to warfarin for stroke prevention in atrial fibrillation patients. Studies have shown that dabigatran is similar to warfarin in rates of stroke prevention and major hemorrhages, but may be advantageous in that there is no need to monitor INR. While significant advancements in stroke management are taking place, it should be noted that rehabilitation and lifestyle modifications remain crucial elements to stroke prevention and functional recovery.
REFERENCES


Author Biography

Lucy Lu is a third year student at the Michael G. DeGroote School of Medicine, McMaster University.