

Stroke due to Other Mechanisms

Prior to making any medical decisions, please view our disclaimer.

Management Algorithm: Stroke due to Other Mechanisms

- Dissection
- Cerebral Venous Sinus Thrombosis
- Hypercoagulability and Hematological Disorders
- Complicated Migraine
- CADASIL
- Vasculitis
- Infection, Endocarditis
- Mitochondrial Cytopathy
- Genetic
- Non-Inflammatory Vasculopathy

Diagnostic Criteria

Clinical scenario or ischemic pattern on neuroimaging which is either not consistent with embolic, large vessel or lacunar etiology, or which suggests an alternative mechanism.

Differential Dx

- Embolic
- Large Vessel
- Lacunar

Dissection

- Sites of injury include intracranial or extracranial carotid or vertebral arteries
- Patients may present with or without ischemic infarction. Asymptomatic patients may be identified by oculosympathetic palsy sparing sudomotor fibers, hypoglossal palsy and periorbital headache (ICA) or severe neck pain (vertebral). Pseudoaneurysm formation should be suspected when lower cranial neuropathy develops late after carotid dissection
- A history of cervical trauma is absent in many cases
- T1 fat-suppression axial MRI of the neck may demonstrate subintimal hemorrhage even in the absence of luminal stenosis
- Consider immediate anticoagulation and re-image at 6-month followup
- Consider stenting or surgery for symptomatic cases failing maximal medical therapy
- Consider possible collagen vascular disease (e.g. Ehler's Danlos) when multivessel dissection or strong family history is present
- Consider renovascular imaging (e.g. MRA) if cerebrovascular imaging suggests fibromuscular dysplasia
- In the absence of collagen vascular disease, recurrent dissection is rare. Most patients return to full levels of activity after a suitable interval (3-12 months) without complications.

Cerebral Venous Sinus Thrombosis

- sites of involvement include the sagittal sinuses, venous sinuses and internal jugular veins
- patients may present with headache, visual disturbance, elevated intracranial pressure, ischemic infarction, hemorrhagic infarction, seizures, encephalopathy
- patients with hypercoagulability, dehydration or craniofacial infection are at increased risk. Presence of CVST should prompt evaluation for these causes.
- Diagnosis is suggested by hyperdensity in torcula on non-contrast CT, and may be confirmed with contrast CT, CT venography, MR venography or Transfemoral angiography.
- Anticoagulation should be started immediately, even in the presence of hemorrhagic infarction. Patients who progress on heparin should be considered for transvenous thrombolysis.

Hypercoagulability and hematological disorders

- Causes of hypercoagulability include malignancy (esp. mucin producing adenocarcinoma), pregnancy (or postpartum period), oral contraceptive use, inherited thrombophilias (esp. protein C, S, Factor V leiden, antithrombin III, prothrombin mutation), antiphospholipid antibodies, end stage renal disease (proteinuria), liver failure, disseminated intravascular coagulation (infection, malignancy, trauma), heparin-induced thrombocytopenia
- Causes of hyperviscosity include leukocytosis (blast crisis), thrombocytosis (ET), erythrocytosis (PV), cryoglobulinemia, Waldenstrom's, sickle cell anemia

- Consider hematology consult and, if appropriate, screening for occult malignancy. Since hypercoagulability of malignancy may be resistant to warfarin, consider LMW Heparins in this setting.
- Consider long term anticoagulation as determined by underlying cause
- Consider family screening if prothrombotic genetic polymorphism detected]

Complicated Migraine, also known as Migrainous Stroke

- In contrast to classic migraine (headache accompanied by transient neurologic symptoms) or acephalgic migraine (transient neurologic symptoms in the absence of headache), complicated migraine is an older terminology used to denote ischemic stroke that occurs in the setting of migrainous symptoms, often in patients with a history of classic migraine.
- The relationship between the migraine and stroke is uncertain, and may be due to vasospasm, hypercoagulability or recurrent neuronal depolarizations (spreading depression). These patients still warrant a full evaluation for embolic sources, but may benefit from migraine prophylaxis which includes antiplatelet therapy and calcium-channel antagonists. Consider avoiding medications which may precipitate vasospasm (e.g., triptans, ergotamines, amphetamines, stimulants, silfenadil) or migraine (oral estrogens).
- Consider genetic and mitochondrial evaluation in families with migraine and stroke or stroke-like episodes (See below)

CADASIL

(cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy)

- CADASIL is an autosomal dominant arteriopathy caused by mutations of the Notch 3 gene on chromosome 19. The main clinical manifestations of the disease include attacks of migraine with aura, mood disturbances, recurrent ischemic strokes, and progressive cognitive decline. CADASIL is the most common hereditary stroke disorder and is likely under-diagnosed worldwide.
- Because of the absence of a curative or CADASIL-specific treatment to date, the management of this chronic cerebral small vessel disease revolves around medications for preventative and symptomatic therapy, genetic counseling, rehabilitation therapy, neuropsychological evaluation, and social work consultation.
- The principle objectives in work-up and evaluation include:
 1. therapy of symptoms associated with the disease,
 2. evaluation and treatment of comorbid illnesses including vascular risk factors,
 3. neuropsychological or cognitive evaluation,
 4. methods to aid patients to maintain autonomy
- **The recommendations for the prevention of stroke in patients with CADASIL** are based on international guidelines for prevention of stroke in general (non-genetic, cardiovascular and cerebrovascular causes). The principle recommendations are :
 1. antiplatelet therapy
 2. treatment of hypertension (if present)
 3. optimal diabetes management (if present)
 4. treatment of hyperlipidemia (if present)
- **Other symptomatic therapy** for conditions associated with the disease or its stroke-related complications :
 1. Migraine : prophylactic therapy for migraine may be necessary in some patients. The current practice recommends avoiding vasoconstrictors for treatment (such as triptans and ergot based medications) based on theoretical risk these medications may pose for cerebral perfusion in patients with compromised cerebral blood flow
 2. Cognitive impairment : a randomized trial of donepezil in patients with cognitive impairment and CADASIL did not support recommendation of donepezil in patients with CADASIL.
 3. Depression : mood disorders associated with the disease should be treated with available medications recommended for these disorders in current practice.
 4. Epilepsy : antiepileptic therapy should be considered in CADASIL patients with partial or generalized seizures
 5. Pain : Pain associated with stroke-associated spasticity or pressure sores (due to immobility) should be treated with physical therapy. Medications for chronic pain control may also be considered. Referral to a specialized pain center should be considered in cases of difficult to control pain.
 6. Pseudo-bulbar palsy : sometimes a consequence of cerebral infarction in CADASIL, anecdotal experience suggests that emotional outbursts (inappropriate crying or laughing) may be controlled with paroxetine. Excessive salivation may be improved with scopolamine.
 7. Urologic and gastrointestinal symptoms : in advanced stages of CADASIL patients may experience urinary symptoms of central origin. In these cases, urologic consultation should be considered. Constipation due to sphincter dysfunction may benefit from recommended medications other therapies for constipation.
 8. Infections : difficulties in swallowing or urinary retention in advanced stages of the disease may result in bronchopulmonary or urinary infections. Appropriate antibiotic or antifungal therapy should be considered.
 9. Spasticity : Antispasmodic medications (such as baclofen) should be considered in cases of CADASIL-associated hypertonia.
- **Medications to avoid or to use with caution in patients with genetically confirmed CADASIL :**
 1. Medications which could cause hypotension should be used with caution in patients with CADASIL due to the possible detrimental effects due to decreased cerebral perfusion. Therapeutic choices during anesthesia should be carefully considered to minimize such potential risks.
 2. Cerebral vasoconstricting agents such as triptans and ergot derivatives should be avoided due to their potential effects on cerebral perfusion (as discussed above under Migraine therapy).
 3. Anticoagulant therapy should be avoided in the absence of specific indications for anticoagulation due to the possible risk of intracerebral hemorrhage in the disease.
 4. In the absence of cerebral large artery occlusion, thrombolytic medication for stroke in CADASIL is should be used with caution due to the possible increased risk of intracerebral hemorrhage in CADASIL.
- Further information is also available through our colleagues at Hôpital Lariboisière (Paris, France) : <http://www.cervco.fr/pathologies/cadasil.0.All.Cadasil.maladies.en.htm>

Non-infectious Vasculitis-Arteritis

Small-medium size arteries

- Granulomatous Angiitis of the CNS presents with headache and subacute mild to moderate encephalopathy, although patients may present with stroke as the initial symptom. TFA may show focal narrowing with abrupt vessel cutoffs and delayed venous phase if the vessels involved are of sufficient diameter to be identified (50 microns?). In other cases, brain biopsy with examination of meningeal vessels is necessary to identify the inflammatory component. Lumbar puncture reveals mild pleiocytosis and elevated total protein, with or without red blood cells. Signs or symptoms of systemic vasculitis are absent. Treatment includes supportive care and immunosuppression (prednisone, imuran, cyclophosphamide).
- Giant Cell arteritis ("Temporal Arteritis") occurs in patients over 60 and is associated with headache, jaw claudication, polymyalgia rheumatica, malaise, fever, weight loss, cranial neuropathies and often anemia. Patients may complain of indurated, tender temporal arteries. It should be considered in any older patient with transient monocular blindness. When the diagnosis is strongly suspected, prednisone 60-80 mg should be started and a temporal artery biopsy obtained within 48-72 hours. There may be a role for ultrasound in the diagnostic evaluation of the temporal artery, and for bilateral biopsy to confirm the diagnosis.
- Systemic Lupus Erythematosus has CNS involvement in up to 75% of cases, mainly in the form of diffuse microangiopathic T2 hyperintensities on MR imaging. Behavioral disturbances, seizures and cranial neuropathies may occur, with stroke-like episodes, peripheral neuropathy, myelopathy and frank psychosis occurring less frequently. Cerebritis may occur without infarction, and may be detected with MR imaging. Treatment includes supportive care and immunosuppression (prednisone, imuran, cyclophosphamide).
- Other rarer causes include polyarteritis nodosa, Wegener's granulomatosis and Behcet's syndrome all of which have peripheral manifestations and less commonly involve the CNS.

Large arteries

Takayasu's arteritis is a disorder of unknown etiology more prevalent in Asian women which affects the aorta and origins of the great vessels. Its propensity to involve the subclavian arteries has led to the eponym, "pulseless disease". TIA or cerebral infarction may occur due to low flow hemodynamics. There is no known treatment aside from cervical artery-to-artery bypass.

Infectious Vasculitis-Arteritis

Tuberculosis and tertiary syphilis cause a pachymeningitis at the base of the brain, leading to occlusive arteriopathy often with associated lower cranial neuropathies. Lumbar puncture for CSF sampling is required for diagnosis, and peripheral manifestations may be lacking late in the disease course (anergy, negative serologies). Mucormycosis may cause stroke by direct vessel invasion or associated inflammatory vasculitis. Viral infections (CMV, VZV, HIV) may cause focal vasculitis and respond to directed antiviral therapy.

Endocarditis

- Infective native valve endocarditis may be due to a variety of organisms including gram positive cocci, gram negative cocci, fungi. Organisms most likely to cause cerebral embolism include staph aureus, strep viridans and enterococci, and the fungi aspergillus and candida species. Mycotic aneurysm (infectious aneurysm) is more common with these virulent organisms and may be due to infected material embolized to the vaso vasorum or to more distal arterial branches with focal intimal invasion. The majority of mycotic aneurysms are located in the distal MCA and ACA territories and are unlikely to be seen with non-invasive imaging. Treatment of endocarditis consists of parenteral antibiotics without the use of anticoagulation, with diagnostic angiography only in selected patients. Angiography may be considered in patients with unexplained neurologic deficits or CT imaging suggestive of cerebritis. Prosthetic valve endocarditis is treated in essentially the same manner, although the risk of thromboembolism must be weighed against the risk of hemorrhagic CNS events, and patients may benefit from continued anticoagulation if they have no evidence of hemorrhage on brain imaging. For patients who develop hemodynamic compromise requiring valve replacement, there is an increased risk of CNS hemorrhage with cardiac surgery that must be weighed against the risk of recurrent emboli and cardiac morbidity. If surgery is to be performed, it may be best to operate early (within 3 days of stroke) or much later (>2 weeks) to minimize the risk of blood-brain barrier dysfunction at the time of surgery.
- Marantic (non-bacterial thrombotic) endocarditis occurs in patients with malignancy (often mucin-producing adenocarcinoma) or connective tissue disease (e.g., SLE) and often coexists with disseminated intravascular coagulation. Treatment is directed toward the underlying lesion, and antiplatelet or anticoagulant therapy may be helpful in preventing further emboli. In some patients with hypercoagulability of malignancy, warfarin may be less effective than the heparins.

Mitochondrial Cytopathy

Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes syndrome (MELAS) is a syndrome which often manifests in adolescence with abrupt onset of stroke-like episodes including alternating hemiparesis, hemianopsia, cortical blindness, focal or generalized seizures. Serum and CSF lactate is increased and is accompanied by CT or MR abnormalities. The presence of "ragged red" fibers on muscle biopsy confirms the diagnosis. Defects in mitochondrial DNA are the cause, and defects in Complex 1 have been associated with MELAS. Treatment is supportive and co-enzyme Q supplementation may be helpful.

Genetic

- Except in the rare cases discussed below, stroke risk is not a monogenic disorder. The genes that increase predisposition to stroke likely reflect generalized systemic factors such as lipid and carbohydrate metabolism, vascular reactivity, coagulation and inflammation.
- Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is a rare stroke syndrome documented in a number of small families. It is often associated with classic migraine and is a progressive ischemic disease without treatment which results in death within 10 years of onset. Some of the inherited thrombophilias (e.g., protein C or S deficiency, prothrombin mutation, factor V Leiden mutation) have been linked to single genes. While these can be the cause of cerebral ischemia, they more commonly present with venous thromboembolism.

Non-inflammatory Vasculopathy

- Moya-Moya disease is characterized by its angiographic appearance, "something hazy like a puff of cigarette smoke drifting in the air", namely proliferation of small vessels at a site of focal narrowing in the supraclinoid ICA and proximal MCA and/or PCA stem. It is usually bilateral although can be asymmetric, and progresses to involve all the basal arteries. TIA or cerebral infarction may occur due to low flow hemodynamics. Hemorrhage due to small vessel rupture is a frequent complication. Treatment consists of hemodynamic management, and a variety of procedures designed to stimulate new vessel formation from the cortical surface (encephaloduroarteriosynangiosis, omental onlay or extracranial to intracranial bypass).
- Conditions such as antiphospholipid antibody syndrome ("Sneddon's Syndrome"), vasospasm after occult subarachnoid hemorrhage, collagen vascular diseases (Ehler's-Danlos, fibromuscular dysplasia, Sjogren's), sympathomimetic use (cocaine, ephedrine, pseudoephedrine, OTC diet preparations, cold medicines, etc) may present with evidence of segmental arterial narrowing on cerebrovascular imaging and ischemic symptoms.

Authoring Information

Reviewed/Approved by: Drs. Singhal, Rost, and Viswanathan

Last reviewed: 4/8/2010

Last updated: 11/1/2012