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Stroke Complicating Systemic Immune Mediated Disorders

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Immune mediated systemic disorders may involve the cerebral blood vessels and cause brain ischemia or hemorrhage. Pertinent causes of stroke associated with immune disorders include cardioembolism due to direct involvement of the heart and its valves by the underlying disorder, vasculopathy and a hypercoagulable state related to the primary disorder, frank vasculitis of the cerebral blood vessels, and an increased rate of atherosclerotic changes in the cerebral vasculature secondary to other organ involvement by the primary disease process. It is extremely important to define the exact pathology involved as treatment options vary. Despite the fact that brain involvement is associated with unfavorable prognosis in many of these disorders, prevention of further cerebrovascular events is a feasible goal in most. Furthermore, specific therapy aimed at the cause of the disease (eg, immunosuppressive therapy in giant cell arteritis) results in greatly improved survival rates in certain disorders.

KEYWORDS immune mediated disorders, vasculitis, cerebrovascular disorders, stroke, systemic lupus erythematosus, antiphospholipid syndrome, anticardiolipin, Wegener's granulomatosis, polyarteritis nodosa, Churg–Strauss disease, rheumatic fever, Takayasu arteritis, giant cell arteritis

Immune mediated disorders (also called connective tissue disorders or collagen–vascular diseases) are multisystem disorders that involve many of the body's organs. The immune system is responsible for the pathological changes that occur in many organs and most of these disorders are considered to be autoimmune. The brain may be implicated in many of these disorders and its involvement may represent the initial symptom of the disease. It is important to emphasize that brain involvement in these disorders may have many facets and cerebrovascular involvement is just one of these. Other forms of brain injury associated with connective tissue disorders include direct involvement by auto-antibodies (ie, auto-immune encephalitis and chorea in systemic lupus erythematosus [SLE]), aseptic meningitis, metabolic encephalopathy secondary to other organ involvement (eg, kidney failure in SLE), and others. These patterns of CNS involvement will not be discussed here. However, it is important to understand that not all forms of CNS involvement in these disorders have similar pathophysiological, prognostic, and therapeutic implication, and therefore, archaic terminologies such as lupus brain or lupus cerebritis are inappropriate.

Cerebrovascular involvement in these disorders can take several forms including cardioembolic strokes secondary to involvement of the myocardium, accelerated atherosclerosis, vasculopathy due to abnormalities in the clotting system, and frank vasculitis (Table 1).

Cardioembolic Strokes Complicating Connective Tissue Disorders

In these circumstances an ischemic stroke results from an embolus originating in the heart. Involvement of the myocardium and the endocardium is quite common in some of these systemic disorders including rheumatic fever (RF) and SLE with or without the antiphospholipid syndrome (APS). The resulting injury to the heart predisposes to the formation of clots, which can then be dislodged and carried in the blood flow to the brain where they can occlude an arterial branch to cause a stroke.

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Table 1 Causes and Treatment of Stroke Related to Systemic Connective Tissue Disorders

Category	Examples	Presumed pathogenesis	Therapy
Cardioembolism	RF, SLE	Cardiac lesions lead to brain emboli	Anticoagulants, immunosuppressive
Vasculopathy leading to stroke	SLE, APS	APLA lead to procoagulable state	Antiplatelets, anticoagulants, anti-inflammatory immunosuppressive
Arterial vasculitis	TA, GCA, PAN, WG, CS, IAC	Cell- or antibody-mediated inflammation in vessel wall	Immunosuppressive stents—surgery (TA)
Venular vasculitis	Behcet's	Cell-mediated inflammation in small venules	Immunosuppressive
Accelerated atherosclerosis	SLE, PAN, PSS	Hypertension, atherosclerotic risk factors	Antiplatelets, antihypertensive
Mechanical compression	RA, AS	Arthritic lesion compress arteries	Immunosuppressive surgery, endovascular stent
Dissection	TA		Endovascular

RF, rheumatic fever; SLE, systemic lupus erythematosus; APS, antiphospholipid syndrome; APLA, antiphospholipid antibodies; TA, Takayasu arteritis; GCA, giant cell arteritis; PAN, polyarteritis nodosa; WG, Wegener's granulomatosis; CS, Churg-Strauss disease; IAC, isolated angiitis of the CNS; PSS, progressive systemic sclerosis; RA, rheumatoid arthritis; AS, ankylosing spondylitis.

RF usually occurs between ages 4 and 18 with an incidence of less than 1/100,000 in developed countries.[1,2] RF-induced heart damage is thought to be secondary to group A Streptococcal infection, leading to target organ damage due to antigenic mimicry.[1,2] Heart valve involvement is the most characteristic and potentially dangerous pathologic effect.[3] However, the exact prevalence of rheumatic heart disease is difficult to ascertain because of lack of standardized diagnostic criteria. The inflammatory process commonly involves the heart valves and leads to valvular edema. Untreated valves can develop thickening, adhesions, and retraction of leaflets and cusps, leading to stenosis or regurgitation. Similar involvement of the chordae can cause regurgitation even without frank valvular involvement.[3] While all valves may be involved, the mitral valve is the most frequently involved followed by the aortic, tricuspid, and pulmonary valves.[4] Furthermore, in the long term both mitral stenosis and regurgitation can cause left atrial enlargement, which may in turn lead to atrial fibrillation (AF). Both rheumatic valve disease and rheumatic AF predisposes to thrombi formation in the left atrium and distal embolization to the brain.[3] Moreover, not infrequently the severity of mitral and aortic valve disease is such that it necessitates valve replacement and mechanical heart valves are known to cause thrombi which can embolize to the brain.[3] Therefore, patients with mechanical valves are usually treated with anticoagulants. This in turn exposes them to both ischemic (when under-anticoagulated) and hemorrhagic (when over-anticoagulated) stroke. The myocardium itself may also be involved in RF as Aschoff bodies are often found in the myocardium and other parts of the heart of patients with carditis. Carditis can in itself also lead to formation of intramural thrombi, which can then embolize to the brain. In summary in patients with RF valvular and myocardial involvement both predispose to clot formation and ensuing brain emboli and ischemic stroke. These patients should be treated with dose-adjusted anticoagulants to prevent stroke[5] as is the case for patients with atrial fibrillation that is unrelated to RF.[6,7] For patients with rheumatic AF and those with valvular disease and no prosthetic valve an INR of 2 to 3 usually suffices but for those with mechanical heart valves the target INR should be set at 3.5. Patients on anticoagulants should be closely monitored to avoid both under- and overtreatment that can be dangerous.

The heart may also be involved in other connective tissue disorders including SLE, which can cause endocarditis.[8-11] This specialized form of carditis known as Libman–Sacks endocarditis can also affect the heart valves and be the culprit for embolic stroke. The frequency of Libman–Sacks endocarditis is assumed to be up to 40% of patients with active SLE. However, most of them do not cause significant valvular disease so the incidence of stroke related to these lesions is unknown. Nevertheless, myocardial involvement in connective tissue disorders is very common and overall probably represents the most common cause of stroke in these disorders.

Vasculopathies Complicating Systemic Disorders

Perhaps the most common cause of stroke related to SLE, stroke secondary to coagulation abnormalities, usually results from the presence of antiphospholipid (APLA; the most common of which is anticardiolipin [ACL]) and lupus anticoagulant [LA]) autoantibodies. Antiphospholipid antibodies have been mostly associated with SLE but may also be present independently without SLE as part of the APS. The latter entails migraine-like headaches, thrombotic events including stroke, and recurrent spontaneous abortions without the systemic effects of SLE.

It is important to note that there is a partial overlap between the tests for anticardiolipin antibody and lupus anticoagulant. However, LA is considered to be more specific as a thrombosis risk factor.[12] Furthermore, ACL only measures some of the antiphospholipid activity, and some auto-antibodies such as those directed against phosphatidylinositol,