Rheumatic Heart Disease and Sneddon's Syndrome

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Background  As the pathogenesis of Sneddon's syndrome is unknown, research for associated disease can facilitate our understanding.

Case Description  Of nine patients with Sneddon's syndrome, three had rheumatic heart disease (mitral valve stenosis, regurgitation, or both) due to rheumatic fever or Sydenham's chorea. Transient anticardiolipin antibodies or positive skin lupus band test were present.

Conclusions  Sneddon's syndrome can have multiple causes. In some patients, rheumatic heart disease is a possible causal association. (Stroke. 1994;25:689-691.)

Key Words  • antiphospholipid antibodies  • skin diseases  • cerebrovascular disorders  • rheumatic diseases

Sneddon's syndrome is characterized by the association of ischemic cerebrovascular disease and generalized livedo reticularis, often called livedo racemosa in the European nomenclature. Lesions of the skin comprise endothelitis, subendothelial cell proliferation, and a late fibrotic stage. The same vasculopathy can occur in medium-sized cerebral arteries. Cerebral thromboangiitis obliterans with generalized livedo racemosa, Divry-Bogaert disease, and Sneddon's syndrome are probably the same process. In the literature, there are two different concepts of Sneddon's syndrome. The first considers the syndrome as an idiopathic and progressive occlusive arteriopathy; the other broadens the etiology to include autoimmune diseases, such as systemic lupus erythematosus (SLE), lupus-like syndrome, or primary antiphospholipid antibody (APLAB) syndrome. Nonetheless, the pathogenesis of Sneddon's syndrome and the pathophysiology of cerebral involvement remain unclear. Thus, the research for associated diseases can be useful. We report the association of Sneddon's syndrome with rheumatic heart disease in three cases among a series of nine patients.

Subjects and Methods

We studied nine patients with Sneddon's syndrome. All had generalized livedo racemosa, strokes or vascular dementia, and multifocal ischemic lesions demonstrated by brain computed tomography or magnetic resonance imaging (MRI). The livedo was a violaceous, irregular, arborescent network of the trunk, buttocks, and limbs. Before treatment, patients underwent the following investigations: research for arterial hypertension, rheumatic fever, smoking, and oral contraceptive use; cerebral angiography; skin biopsy; electrocardiography; trans-thoracic two-dimensional echocardiography (TTE); and laboratory tests. The laboratory investigations included proteinuria, erythrocyte sedimentation rate, glycemia, cholesterol, creatinine, antinuclear antibodies (ANA), complement fractions 3 and 4, fibrinogen, activated partial thromboplastin time, cryoglobulins, syphilis serology, and immunoglobulin G isotype anticardiolipin antibody (ACAb) by a standardized enzyme-linked immunosorbent assay (ELISA).

Case Reports

The 9 patients in our series included 1 man and 8 women aged 25 to 59 (mean, 39.6) years at the onset of strokes. Three had rheumatic heart disease. Their histories are detailed below. Details concerning the 6 others will be published elsewhere, but 2 had ANA (1 with mitral valve thickening) and 3 had transient APLAb. In the 3 patients with rheumatic heart disease, there was no fever and cardiac rhythm was normal. Unless specified, all the laboratory tests described above were normal.

Case 1

When she was 12, the patient developed rheumatic fever after pharyngitis. She received steroids and penicillin. At 15, after an infection, she had 2 months of Sydenham's chorea. She again received steroids and penicillin. At 21, because of dyspnea and a cardiac murmur, mitral valve stenosis was diagnosed. She underwent commissurotomy at 29. Between 21 and 34, she had three spontaneous abortions. At age 33, Raynaud's syndrome and generalized livedo racemosa appeared. She did not smoke or use oral contraceptives. She was referred at age 35 because of progressive dysarthria and intellectual impairment. Examination disclosed agraphia, acalculia, apraxia, and right pyramidal syndrome. Intelligence quotient was 60. Brain MRI showed ventricular enlargement, left parietotemporal cortical atrophy, and a lacune in the left thalamus. On cerebral angiography, there were bilateral distal occlusions of the middle cerebral artery (MCA), with an abnormal collateral network distally (Fig 1A). Cerebrospinal fluid contained 1 leukocyte per cubic millimeter and 0.49 g/L protein, with 18% oligoclonal immunoglobulin G. Blood pressure was normal. Cardiac murmur was present, and TTE showed aortic valve regurgitation, mitral valve regurgitation, and stenosis (mitral valve surface, 1.5 cm²). Cardiac ventricles and atria were...
not distended. Valvular or mural thrombi were not seen. Skin biopsy showed fibrosis of dermal capillaries. During the 19 months of follow-up, two of five ACAb determinations were positive. Because of mild proteinuria, renal biopsy was performed. It showed severe medial and intimal hyperplasia (Fig 2A and B), with stenosis or occlusions of glomerular arterioles. The patient received coumadin and azathioprine with stabilization of her neurological status.

**Case 2**

When she was 17, the patient had rheumatic fever after an infectious pharyngitis. She received steroids and penicillin. At 24, a generalized livedo racemosa appeared. At 27, because of cardiac murmur, mitral valve stenosis was diagnosed. She had Raynaud's syndrome. At age 30, mild arterial hypertension was discovered. She was a cigarette smoker and did not use oral contraceptives. Between 25 and 40, she had many attacks of left hemiparesis and migraine-like episodes with cephalalgia and scotoma. At 40, she was referred to our hospital because of persistent left hemianopsia. Brain MRI showed right insular and occipital infarcts. Cerebral angiography disclosed loss of insular branches in the right MCA and distal occlusion of the right pericallosal artery with a collateral network (Fig 1B). Cerebrospinal fluid was normal. Under treatment, blood pressure was normal. Cardiac murmur was present. TTE showed mitral valve regurgitation and stenosis (surface, 1.5 cm²). Aortic valves were normal. Enlargement of the left atrium indicated a hemodynamically significant mitral valve lesion. Valvular or mural thrombi were not seen. Skin biopsy showed fibrosis of dermal capillaries and slight endothelitis. During the 27 months of follow-up, one of four ACAb determinations was positive. She received coumadin with stabilization of her neurological status.

**Case 3**

Patient 3, a woman, had rheumatic fever after an infectious disease at age 13, for which she received steroids and penicillin. A few months later, a cardiac murmur was discovered. She had migraine headaches and Raynaud's syndrome. She was a cigarette smoker and used oral contraceptives. At 42, generalized livedo racemosa appeared. She complained of slight migratory joint pains. At ages 46 and 47, because of two episodes of transient aphasia and apraxia, she was referred to our hospital for evaluation. Brain MRI showed infarcts in the right frontal lobe and the left hemispheric white matter. Cerebrospinal fluid examination and cerebral angiography were normal. Blood pressure was normal. TTE showed mitral valve regurgitation and peripheral valvular thickening without stenosis. The aortic valves...
were normal, and the ventricles and atria were not distended. There were no valvular or mural thrombi. Skin biopsy disclosed fibrosis of dermal capillaries. Results of an immunofluorescent lupus band test were positive, with anti-immunoglobulin M antibodies. ANA were negative. None of the four ACAB determinations performed during the 26 months of follow-up were positive. She received aspirin without recurrence of stroke.

**Discussion**

Our three patients had generalized livedo racemosa and cerebrovascular disease. Brain MRI showed multifocal ischemic lesions. In two patients, cerebral angiography displayed multiple distal arterial occlusions with capillary collateral network. Dermal capillaries showed fibrosis, with slight endothelitis in one case. These data correspond to the diagnostic criteria for Sneddon's syndrome. Migraine, mild arterial hypertension, or smoking were present as in previous series. In addition, they had rheumatic heart disease after rheumatic fever or Sydenham's chorea. Valvulopathies (mitral valve stenosis, regurgitation, or both) appeared several years before the first manifestations of Sneddon's syndrome and were hemodynamically severe enough to induce left atrium enlargement in one case and to necessitate commissurotomy in another one. The association of Sneddon's syndrome and rheumatic heart disease has been reported in an isolated case. One series mentioned cardiac murmurs but without further specifications. Other series did not focus on valvulopathies in Sneddon's syndrome. Was rheumatic heart disease relevant to the pathophysiology of Sneddon's syndrome? Systemic vasculopathies such as Sneddon's syndrome are not common after rheumatic fever or Sydenham's chorea, but without prospective studies no definite conclusions can be reached. The high proportion of rheumatic heart disease in our series (three of nine patients) suggests that this association is possibly not fortuitous.

If the hypothesis is correct, the links between Sneddon's syndrome and rheumatic fever or Sydenham's chorea should be discussed. In our cases, cerebral angiography suggested that strokes depended on distal obliterations of the cerebral and leptomeningeal arterioles by a local vasculopathy, which has been proved to be an aspecific obliteratoris endarteritis in pathological cases, also found in the skin and in the glomerular arterioles in case 1. Burton discusses the responsibility of a local coagulation anomaly of various causes, possibly induced by microemboli from the left atrium in the case of rheumatic heart disease. Moreover, some of our patients had spontaneous abortions, Raynaud's syndrome, positive lupus band test on skin biopsy (case 3), or fluctuating ACAB (cases 1 and 2). These anomalies are found in SLE or in ACAB syndrome, in which generalized livedo racemosa and strokes can occur, sometimes with intimal cell proliferation of medium-sized cerebral arteries. APALAB and skin immunoglobulin M deposits could be related to rheumatic heart disease, and ACAB have been reported in patients with valvulopathies of various etiology, suggesting that they can be produced after any valvular lesions. Links between SLE, lupus-like syndrome, ACAB syndrome, and rheumatic fever have also been suggested in patients with ACAB. Although inconclusive, our data suggest that Sneddon's syndrome can be related to rheumatic heart disease, but the pathophysiology of vascular lesions remains unclear.

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