

## Sneddon's syndrome with anticardiolipin antibodies — complications and treatment

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**Abstract** We investigated 2 patients with Sneddon's syndrome, elevated anticardiolipin antibodies and systemic complications, which included stroke, habitual abortions, cardiac valvular lesions, acrocyanosis, hypertension and renal insufficiency. Treatment with a combination of immunosuppressive agents and warfarin or aspirin prevented further complications and improved renal function. It is important for those in different specialties to be aware of this potentially treatable disorder.

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In 1965, Sneddon<sup>1</sup> described 6 patients with a combination of severe livedo reticularis (LR), cerebrovascular incidents and mild hypertension. He postulated that the underlying pathology in such patients is endarteritis obliterans, even though most skin biopsies are normal or show nonspecific changes.<sup>2,3</sup> An association between antiphospholipid antibodies (APAs) and LR was reported in 1984 by Hughes<sup>4</sup> in patients with systemic lupus erythematosus, and by Jonas *et al.*<sup>5</sup> in 1986 in patients with Sneddon's syndrome. Subsequent reports established an association, particularly for anticardiolipin antibodies (ACAs) and Sneddon's syndrome. It also became apparent that these patients might develop other complications, including habitual abortions, arterial and venous thrombosis, haemolytic anaemia and disturbed peripheral circulation.<sup>6-8</sup> Treatment of this condition remains controversial and antiplatelet agents, anticoagulants, immunosuppression, splenectomy and plasmapheresis have all been used, with variable results.<sup>9,10</sup>

We report on 2 patients with positive serum ACAs and Sneddon's syndrome who responded well to immunosuppression.

### Case reports

#### Case 1

A 34-year-old white woman, who had suffered a left-sided stroke 5 years earlier, presented in January 1989. She had a history of 8 pregnancies of which 7 had spontaneously aborted. The 5th pregnancy had lasted until the 28th week and she had given birth to a healthy premature infant. Clinical examination confirmed the left-sided hemiparesis. She had marked generalised racemose LR and acrocyanosis; a clinical diagnosis of Sneddon's syndrome was made. Laboratory investigations revealed the following abnormalities: serum creatinine level 124,6  $\mu\text{mol/l}$  (normal range 67 - 97  $\mu\text{mol/ml}$ ), total complement 134 micro.complement haemolysed

units per millilitre serum ( $\mu\text{CH U/ml}$ ) (normal range 150 - 200  $\mu\text{CH U/ml}$ ) with normal C3 and C4 values, a partial thromboplastin time (PTT) of 35,4 seconds (normal range 24 - 36 seconds), and positive reagen flocculation and *Treponema pallidum* haemagglutination (TPHA) test results. The fluorescent treponemal antibody absorption test (FTA-ABS) was positive for immunoglobulin G (IgG), but not for IgM. A skin biopsy from a livedoid area on the arm was normal. Computed tomography (CT) of the brain showed infarcts in the distribution of both middle cerebral arteries. The patient was treated with aspirin 300 mg daily and became pregnant 5 months later. Prednisone 60 mg/d was given in addition to the aspirin,<sup>10</sup> but unfortunately she aborted at 10 weeks' gestation. Prednisone was tapered and stopped, but after 10 days without prednisone she suffered an acute exacerbation of her previous left-sided stroke. Laboratory investigations produced results similar to those at first admission with the following exceptions: negative serological tests for syphilis (STS) and positive ACAs with a titre of 1:68 (normal range 1:40). She was negative for lupus anticoagulant (LA) as assayed by means of the dilute tissue thromboplastin test.<sup>11</sup> Echocardiography revealed slight mitral incompetence without valvular vegetations or chamber dilatations. CT of the brain showed infarcts in the right anterior cerebral and the right and left middle cerebral artery distributions (Fig. 1).

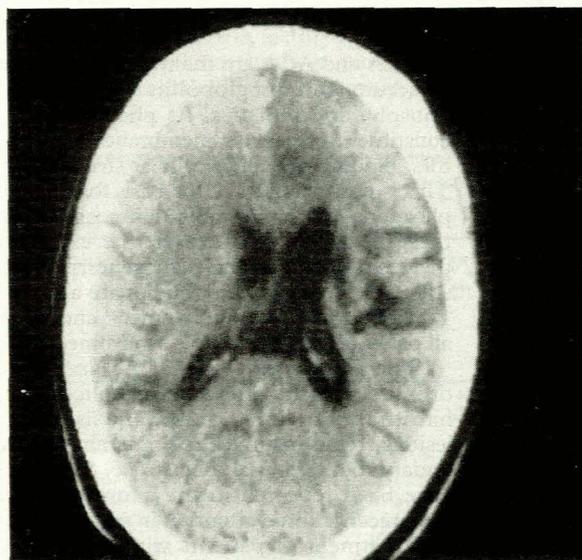


FIG. 1 Computed tomographic scan of the brain showing infarcts in the right anterior cerebral and right and left middle cerebral artery distributions.

The acrocyanosis responded well to nifedipine 10 mg twice daily and captopril 12,5 mg twice daily. Immersion of the hands for 10 minutes in warm water alleviated the cyanosis, but left bright red markings where the livedo changes had taken place. Treatment was started with warfarin and azathioprine 50 mg twice daily. Follow-up over 3 years showed no further exacerbations of her disease and serum creatinine levels normalised, but she remained cognitively impaired.

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## Case 2

A 33-year-old white woman presented with a history of hypertension, classic migraine for 4 years, temporal lobe epilepsy with onset 3 years previously and ataxia, with a tendency to fall to the right. Since 1983 she had had 5 spontaneous abortions during the first or second trimesters of pregnancy. She had 1 child, born at term in 1980. She smoked an average of 20 cigarettes per day and was taking carbamazepine and captopril.

Examination revealed a blood pressure of 170/100 mmHg, acrocyanosis of the hands and feet which abated on immersion in warm water, and severe generalised racemose LR. The findings on neurological examination were normal, as was a full blood count, the erythrocyte sedimentation rate, levels of auto-antibody, immunoglobulin and total complement, and the cerebrospinal fluid. Serological testing for syphilis was negative. The serum urea level was 7.4 mmol/l (normal range < 6.4 mmol/l) and creatinine clearance 72 ml/min; prothrombin activity and partial thromboplastin time were normal on two occasions. She was negative for LA and ACA-positive in a titre of 1:62. Heart echocardiographic assessment showed mild mitral and tricuspid valve incompetence, electro-encephalography revealed a right posterior temporal lobe epileptiform dysfunction and magnetic resonance imaging of the brain showed three small infarcts: 1 occipital, 1 in the right temporal lobe and 1 in the left cerebellum.

The patient was treated with azathioprine 50 mg twice a day, prednisone 15 mg/d, aspirin 325 mg/d and nifedipine 10 mg 3 times a day. Follow-up at 6 months showed no evidence of further strokes. Serum urea and creatinine values normalised, but she still had hypertension and moderate acrocyanosis.

## Discussion

The LA and ACA are the two best characterised groups of serum immunoglobulins (IgG or IgM) that bind phospholipid moieties. As phospholipids are a major constituent of cellular membranes and coagulation factors, binding may alter cellular structure and function.<sup>12</sup> This is postulated to be the basis for the numerous complications and abnormal blood coagulation observed in these disorders.<sup>6-8</sup> However, the exact importance of these antibodies in the pathogenesis of the disorders is still unclear, as these antibodies are also present in up to 11% of normal pregnant women<sup>13</sup> and are not present in all patients with Sneddon's syndrome.

The 2 patients with ACAs and Sneddon's syndrome<sup>6,7</sup> had the following complications: stroke, LR, habitual abortions, acrocyanosis, cardiac valvular lesions, renal insufficiency, migraine and epilepsy secondary to a temporal lobe stroke. Similar complications have been reported in the neurology literature,<sup>6,7</sup> but have received little attention in general medical journals.

Treatment of patients with APA without an associated auto-immune disorder remains controversial.<sup>7,14</sup> Patients treated with oral anticoagulation and antiplatelet agents have had variable clinical responses. An apparent association between ACA titres and thrombotic symptoms has prompted the use of immunosuppressive treatment.<sup>15</sup> Asherson *et al.*<sup>16</sup> reported on 6 patients who had ACA-associated thrombotic events after cessation of warfarin therapy even though they were still receiving prednisone and azathioprine at the time. All had raised ACA levels at the time of recurrence; this supports the theory of an association between raised APA levels and thrombotic tendencies. There was a close temporal relationship between the withdrawal of prednisone therapy and recurrence of stroke in patient 1. This suggests that cessation of immunosuppressive

therapy can result in a rebound increase in thrombotic complications, which is not prevented by the simultaneous use of antiplatelet agents. It therefore seems appropriate to monitor ACA titres and LA activity, especially postpartum or postabortion, before immunosuppressive or anticoagulant therapy is reduced. Our patients had no further recurrences of thrombotic complications and both showed improvement of renal function on a combination of azathioprine and warfarin or azathioprine and low-dose prednisone and aspirin.

Lubbe *et al.*<sup>10</sup> used prednisone to suppress maternal LA in 6 pregnant patients, 5 of whom gave birth to live infants. Unfortunately, prednisone treatment did not prevent abortion in patient 1. It is not clear if prednisone therapy is more beneficial in patients with LA than in those with ACAs. Campbell *et al.*,<sup>17</sup> however, used a combination of warfarin and prednisone successfully in a pregnant patient with ACAs.

In patient 1, initially positive serological tests for syphilis became negative after prednisone therapy. The specific treponemal antibody tests (FTA and TPHA) can be false-positive in the presence of APA and since prednisone therapy would not normalise a true positive test for syphilis, this confirmed the initial false-positivity of these tests. Surprisingly, previous workers did not address this potentially confusing issue, for strokes, habitual abortions, LR and even ACAs can all occur as complications in syphilis.

In both patients severe acrocyanosis threatened the viability of fingers and toes. The response to warming of extremities in water and to treatment with calcium channel blockers indicated that this was at least partially induced by vasospasm. As steroid therapy might aggravate vasospasm, particularly in patients with underlying vasculitis,<sup>18</sup> it is important to treat the acrocyanosis symptomatically, in addition to the therapy aimed at the primary disease.

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