Background  Sneddon’s syndrome is a disease characterized by livedo reticularis and cerebrovascular lesions, with a hereditary transmission and unknown etiopathogenesis. A number of reports have documented a link between antiphospholipid antibodies and Sneddon’s syndrome with different results. The present work was designed to sequentially study antiphospholipid antibodies in a patient with Sneddon’s syndrome and her family and their potential role in thrombotic events. We used cardiolipin and a mixture of phospholipids from rabbit brain as antigen for antiphospholipid assays to determine diagnostic usefulness.

Case Descriptions  A patient with Sneddon’s syndrome and 12 available family members belonging to three generations were evaluated to determine the presence of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) during vascular thrombotic events and asymptomatic periods.

Conclusions  Our results support a temporal relation between thrombotic events in Sneddon’s syndrome and lupus anticoagulant; anticardiolipin antibodies remained invariable. Our index case patient and her father could be diagnosed as having primary antiphospholipid antibody syndrome. Aspirin was not effective in preventing thrombosis. After the onset of oral anticoagulant therapy, no recurrences were seen. The use of a mixture of phospholipids as antigen could present some advantages in serological studies performed in antiphospholipid syndromes. (Stroke. 1994;25:1071-1074.)

Key Words  •  anticoagulants, lupus  •  anticoagulants, antiphospholipid antibodies  •  cerebrovascular disorders

Sneddon’s syndrome (SS) is a disorder, more common in females, characterized by livedo reticularis (LR) and ischemic cerebrovascular lesions, with a hereditary autosomal dominant transmission or a familial vascular disease suggested in other cases. LR may precede the onset of stroke by years, and the ischemic events are usually repeated.

The histological pattern is a widespread noninflammatory arteriopathy involving small and medium-sized arteries. The etiopathogenesis of this disorder is still unknown. A number of reports have documented a link between antiphospholipid antibodies (aPLs), including lupus anticoagulant (LA) and anticardiolipin antibodies (aCLs), and thrombotic events with different results. These discrepancies may be due to the lack of standardized laboratory tests and the fact that the studies were not carried out at the time of the disease (asymptomatic rather than symptomatic periods). It is now clear that a proportion of patients previously diagnosed with SS are in fact examples of patients with primary antiphospholipid syndrome (PAPS).

In this article we report the coagulation and serological studies of a woman with SS and her family in which aPLs (LA and aCLs) were determined. In our patient the studies were performed during asymptomatic and symptomatic periods.

Subjects and Methods

Thirteen available members (6 males, 7 females; age range, 10 to 72 years) belonging to three generations of the family of an SS patient were studied to determine the presence of LA and aCLs. All were white, with no history of consanguinity.

In addition to a full medical history, all members were specifically questioned with regard to migraine episodes, pos-sible transient ischemic attacks, thrombosis, livedo, smoking, any drug therapy including oral contraceptives, and miscarriages.

Serum and plasma samples were obtained and kept at −70°C until tested. As a control group, 50 healthy volunteers aged 18 to 65 years were used.

Coagulation Tests

Activated partial thromboplastin time (APTT) and prothrombin time (PT) were performed as usual. If the APTT was abnormal, the diagnosis of LA was investigated by performing tissue thromboplastin inhibition time (TTI) and diluted Russell’s viper venom time (dRVVT).

We considered the following criteria for diagnosing LA activity: (1) a prolonged APTT (>6 seconds longer than the higher limit of normal), (2) a positive TTI, and (3) a prolonged dRVVT. Every patient had a normal thrombin time.

The aCL assays were performed by an enzyme-linked immunosorbent assay (ELISA). A titer higher than 13 MPL and 17 GPL U was considered pathological (2.6 SDs over normal volunteer levels). The assay used to detect LA other than cardiolipin of immunoglobulin (Ig) G and IgM subtypes was determined with a mixture of phospholipids used in APTT reagent from rabbit brain (Automated APTT, Organon Teknika Corp) using ELISA with goat anti-human anti-IgG or anti-IgM and peroxidase-labeled goat antihuman IgG antibodies.

Study of Antiphospholipid Antibodies in a Patient With Sneddon’s Syndrome and Her Family

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13 available family members belonging to three generations of the family of the index case patient and her father were studied to determine the presence of antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies) during vascular thrombotic events and asymptomatic periods. The aCL assays were performed by an enzyme-linked immunosorbent assay (ELISA). A titer higher than 13 MPL and 17 GPL U was considered pathological (2.6 SDs over normal volunteer levels). The assay used to detect LA other than cardiolipin of immunoglobulin (Ig) G and IgM subtypes was determined with a mixture of phospholipids used in APTT reagent from rabbit brain (Automated APTT, Organon Teknika Corp) using ELISA with goat anti-human anti-IgG or anti-IgM and peroxidase-labeled goat antihuman IgG antibodies.
anti-IgM marked with alkaline phosphatase (a positive value was defined if absorbance was 2.6 SDs above the mean control optical density).

Other Studies
Additional tests were performed, including serum glucose, electrolytes, renal and hepatic function tests, cholesterol, triglycerides, white cell and platelet counts, hemoglobin and hematocrit, erythrocyte sedimentation ratio, serum complement and immunoglobulin levels, and VDRL and fluorescent treponemal antibody serology for syphilis. Assays for antinuclear antibodies, anti-DNA antibodies, several non-organ-specific antibodies, rheumatoid factor, and anti-streptolysin O antibodies were also performed.

Diagnosis of SS was performed by using clinical criteria, computed tomographic (CT) scan and magnetic resonance imaging (MRI) of the brain on a 1.5-T Somaton (Siemens), and digital artery biopsy.

Case Reports
Case 1
The index case patient (II2 in the Figure) is a 45-year-old woman without a history of obstetric complications. She developed LR predominantly in the lower limbs, focal neurological symptoms of the left hemisphere with relief, seizures, migraine, Raynaud’s phenomenon, and vertigo. She was treated with antiepileptic drugs. A digital artery biopsy demonstrated a noninflammatory arteriopathy. She was then diagnosed with SS and received low doses of aspirin.

The patient was admitted to our hospital because of sudden development of paresthesia and paraisis in her legs and intermittent back pain. On physical examination we found a level sensitive to pinprick at the T10 dermatome; deep tendon reflexes were increased in her right side. She exhibited acrocyanosis (mainly of distal distribution) and marked generalized LR. The rest of the general examination was normal. We suspected a diagnosis of spinal vascular occlusion. Two samples obtained during asymptomatic and symptomatic periods were examined to determine the presence of LA activity and aCLs (Table 1). At the time of her admission, LA activity (IgG subtype) was detected, whereas aCLs remained at the same level as during the asymptomatic period. A brain CT scan showed multiple infarcts in right frontal and cerebellar hemispheres and in the left parieto-occipital area. An echocardiogram and a carotid Doppler showed no alterations. She began acenocoumarol therapy 5 days later, and the neurological deficit improved during her hospitalization. On the 20th hospital day, when she was asymptomatic, a spinal MRI disclosed no abnormalities. At the present time, after 12 months of oral anticoagulant therapy, the patient is well, without evidence of recurrent thrombotic events.

Case 2
The 72-year-old father of the propositus (II in the Figure) suffered an acute myocardial infarction 3 years ago. Hypertension and non-insulin-dependent diabetes mellitus were diagnosed at that time. Two aortocoronary bypasses were performed, a pacemaker was implanted, and aspirin treatment was initiated. In March 1993 he developed unstable angina pectoris because of a subtotal bypass occlusion. At this time LA activity (IgG subtype) was evidenced (Table 2). Oral anticoagulant therapy was initiated 20 days later, and he remained asymptomatic for 8 months. He did not present any history of LR, transient ischemic attacks, or stroke.

Results
In view of the presence of aPLs (LA and/or aCLs) in father and daughter, a study of all other available members was undertaken (Table 2). One member was not tested (II3) because of death from leukemia some years ago. A niece of the index case patient (III2), aged 19 years, had developed LR in the lower limbs 2 years before, with no neurological symptoms. In coagulation tests she had a prolonged APTT and positive dRVVT, but TTI was negative. aCLs were positive at low levels (20 GPL and 27 MPL U/mL). In coagulation studies, only two family members (II1 and II9, aged 17 and 11 years, respectively) exhibited LA activity (LA and aCLs of the IgM subtype). The other family members were asymptomatic, and clotting and serological tests for LA were negative. However, aCLs of the IgM subtype were found in some family members (Table 2). In all family members, including case patients 1 and 2, routine tests showed normal parameters.
Table 2. Clinical Status and Serological Data for Family Members

<table>
<thead>
<tr>
<th>Pt/Sex/Age, y</th>
<th>Clinical Status</th>
<th>Coag Test</th>
<th>IgG</th>
<th>IgM</th>
<th>IgG, GPL U</th>
<th>IgM, MPL U</th>
</tr>
</thead>
<tbody>
<tr>
<td>I1/M/72</td>
<td>Myocardial Infarction</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I1/M/47</td>
<td>Well</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I2/F/45</td>
<td>Sneddon’s syndrome</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>I4/F/36</td>
<td>Well</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>27</td>
</tr>
<tr>
<td>I1/F/20</td>
<td>Well</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>I2/F/19</td>
<td>Livedo reticularis</td>
<td>±</td>
<td>-</td>
<td>-</td>
<td>20</td>
<td>27</td>
</tr>
<tr>
<td>I3/M/17</td>
<td>Well</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>I4/M/18</td>
<td>Well</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I5/F/17</td>
<td>Well</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>40</td>
</tr>
<tr>
<td>I6/F/16</td>
<td>Well</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>33</td>
</tr>
<tr>
<td>I7/F/10</td>
<td>Well</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>30</td>
</tr>
<tr>
<td>I8/M/12</td>
<td>Well</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>I9/M/11</td>
<td>Well</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>60</td>
</tr>
</tbody>
</table>

Pt indicates patient; LA, lupus anticoagulant; aCLs, anticardiolipin antibodies; Coag, coagulation; and Ig, immunoglobulin.

Discussion

Levine and Welch first described a patient with SS in whom the LA and aCLs were documented. In contrast, some authors did not find LA or aCLs in their patients with SS. Several small series that appeared in the past few years have associated LA and/or aCLs with neurological diseases including stroke, transient ischemic attacks, seizures, migraine, chorea, LR, and ocular ischemia. Levine et al thus revised the spectrum of neurological diseases associated with aPLs. The clinical combination of thrombotic events with the presence of aPLs, often accompanied by thrombocytopenia, was considered PAPS. For the first time, Levine et al questioned whether SS must be considered PAPS. Our index case patient and her father, according to the above criteria, should be diagnosed with PAPS.

The etiology of PAPS remains obscure. It has been suggested that aCLs could be pathogenically related to this syndrome. Serial studies to determine the presence of aPLs (aCLs and LA) in the same patient with SS or PAPS (in symptomatic and asymptomatic periods) have rarely been performed. In the index case patient, we found LA activity (IgG subtype) at the same time as the spinal thrombosis. In contrast with other authors, who found that the incidence of thrombosis is proportional to the aCL level, we were not able to observe any relation between aCLs and thrombosis (aCL subtype IgM remained at the same level in both periods). Also in case 2, coronary thrombosis appeared concomitantly with LA (IgG subtype) without aCLs. Eight asymptomatic family members had aCLs of the IgM subtype.

It is known that in a few cases SS presents an autosomal pattern of transmission. In the last few years premature stroke and recurrent cerebral infarctions in two families associated with LA and/or aCLs have been reported. As in the family we investigated, these observations suggest the intervention of genetic factors in the development of SS and PAPS.

The propositus and her father were taking aspirin when they developed transient ischemic attack and myocardial infarction, respectively, and we initiated oral anticoagulant therapy at high-intensity levels (international normalized ratio between 3 and 4), in accordance with the conclusions of Rosove and Brewer. After 12 and 8 months our patients remain well.

This family is highly interesting for several reasons. First, a high incidence of aPLs occurred at a young age in symptomatic and asymptomatic individuals. The young asymptomatic members with aPLs, as well as the young patient with LR, must consequently be advised because LR and aPLs may precede the onset of stroke. Second, the presence of LA activity (IgG subtype) appeared concomitantly with transient ischemic attack in the index case patient, while aCLs remained invariable. Third, thrombotic events developed when the patients were on aspirin therapy; after the onset of oral anticoagulant therapy, no recurrences were observed. Fourth, our patient and her father could be considered to have PAPS.

In conclusion, when PAPS or SS is diagnosed, the presence of aPLs must be determined in these patients during symptomatic and asymptomatic periods and in their pedigree. Therapy before thrombosis is very difficult to assess, but after the first thrombotic event, high-intensity oral anticoagulant therapy is probably the best therapy for those patients.

In accordance with Levine et al, we believe that an international SS cooperative study group is necessary. Additional studies should be undertaken to assess the management of patients with SS.

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