Sneddon's Syndrome: Diagnosis by Skin Biopsy and MRI in 17 Patients

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Background and Purpose: Sneddon's syndrome, characterized by generalized livedo racemosa and cerebrovascular lesions, is an underdiagnosed disease. We evaluated clinical, laboratory, histological, and neuroradiological findings in a series of 17 patients to improve diagnostic criteria for Sneddon's syndrome.

Methods: Patients with generalized livedo racemosa and cerebrovascular events were included in the study. All underwent neurological and dermatological examination, skin biopsy, computed tomographic scan, magnetic resonance imaging as well as magnetic resonance angiography, sonography of the extracranial arteries, and a comprehensive laboratory protocol.

Results: Completed stroke was present in eight patients, and 15 reported transient neurological deficits. Magnetic resonance imaging yielded cerebral abnormalities in 16 of 17, whereas computed tomographic scans were abnormal in only 12 of 16 patients. Magnetic resonance imaging revealed more lesions in individual patients than did computed tomography. Magnetic resonance angiography demonstrated patent intracranial vessels in 16 of 17 patients. Skin biopsy showed distinct histopathological findings in all patients. The involved vessels were small to medium-sized arteries at the border between dermis and subcutis. Early inflammatory reactions were followed by subendothelial proliferation and a late fibrotic stage. Laboratory examinations showed impaired creatinine clearance in eight patients, whereas all other laboratory tests, including antiphospholipid antibodies, were normal.

Conclusions: In this series, magnetic resonance imaging and skin biopsy were useful for confirmation of the diagnosis of Sneddon's syndrome. Magnetic resonance findings were not specific, but the high sensitivity for detection of asymptomatic brain lesions helped to confirm the diagnosis in patients with transient symptoms. Histological features of skin biopsies were characteristic if appropriate techniques were employed. (Stroke 1993;24:685–690)

Key Words • cerebrovascular disorders • skin diseases

Sneddon's syndrome (SS) is a rare disease, with only 126 patients reported in the literature as of 1992.1-29 The small number of cases may reflect the unfamiliarity with the syndrome rather than a true reflection of its incidence.30

The diagnostic hallmarks of SS are generalized livedo racemosa (GLR) and stroke.1-2 GLR represents a striking violaceous, netlike patterning of the skin (Figure 1) similar to the familiar sign of livedo reticularis from which it differs by its shape (irregular, broken circular segments, resulting in a seemingly larger pattern), localization (both trunk and extremities), and persistence on warming. In English usage, both types of livedo are termed "reticularis" despite their different pathophysiological basis and prognostic significance: both are caused31 by reduced blood flow and thus lowered oxygen tension, which is lowest at the peripheries of the skin segments supplied by individual central arteries, which then appear as dark, livid rings. Livedo reticularis results from regional or generalized reduction of blood flow (usually due to functional factors such as vasoconstriction in the cold, "cutis marmorata") and thus displays a regular netlike pattern; GLR, in contrast, results from irregular focal and persistent impairment of the blood flow that is physical in nature, such as arterial occlusion in atherosclerosis, vasculitides, or SS.

Because no specific test for SS exists, the clinical differentiation from other phenomenologically similar disorders may be difficult and has raised significant controversy.3,8,14,16,17,32,33 Recently, characteristic histopathological findings have been reported from skin biopsies of patients with SS.34 These consisted of inflammatory changes in the endothelium (endothelitis) of small arteries and were followed by subendothelial cell proliferation leading to partial or complete occlusion. Although these findings are characteristic, skin biopsy cannot confirm SS unless cerebral involvement is documented.

In the past, computed tomography (CT) and x-ray angiography were used to support the diagnosis of SS. Today, magnetic resonance imaging (MRI) has better sensitivity in the diagnosis of subtle cerebral vascular lesions. In addition to MRI we used a high-resolution,
noninvasive, magnetic resonance angiography (MRA) protocol to evaluate the diagnostic potential of combined MRI and MRA in SS.

We report the clinical, histological, and neuroradiological findings of 17 patients suffering from SS and define more precise diagnostic criteria for this disease.

Subjects and Methods

For this study we reinvestigated 17 patients (15 women and two men) with known SS using a standardized clinical and laboratory examination protocol. The age at onset of nonspecific neurological symptoms varied from 16 to 35 (mean, 24.8) years, while clinically apparent symptoms of central nervous system involvement were observed at a mean age of 31.6 (range, 19–45) years. GLR was first noticed by the patients between the ages of 19 and 48 (mean, 28) years, and first documentation in medical reports ranged from 21 to 58 (mean, 34.8) years of age. The mean age at the time of diagnosis was 35.8 (range, 24–58) years. Duration of disease ranged from 2 months to 11 years (mean, 3.9 years).

Diagnosis of SS was based on the presence of GLR; characteristic histopathological vascular changes in skin biopsies; and cerebral involvement as evident from history, neurological examination, and CT scan.

Skin biopsies were performed according to the recommendations of Copeman and Zelger et al; biopsy cones were obtained from the normal-appearing center of the skin lesions with a diameter of 1–2 cm, including subcutis, and were histologically processed in serial sections.

CT, MRI, and MRA scans were analyzed independently by two neuroradiologists, both of whom had been informed of clinically suspected cerebrovascular disease in these cases. CT scans were available for 16 of 17 patients and MRI in all cases. CT examinations were done on a fourth-generation scanner (Somatom Plus, Siemens, FRG) and MRI on a 1.5-T Magnetom (Siemens). The magnetic resonance protocol consisted of T1- and T2-weighted multislice spin-echo sequences in sagittal, transverse, and coronal orientations. A three-dimen-

sional gradient echo sequence with incorporated motion-compensating gradients for constant velocities in slice select and read-out direction was used for MRA. A 64-mm volume was excited in transverse orientation, centered at the circle of Willis, and divided into 64 1-mm slices by an additional phase-encoding gradient. The individual images were reviewed for vessel patency and reconstructed by a previously described ray-tracer algorithm to render projectional angiograms from arbitrary viewing angles. X-ray angiography was available for three patients (patients 1, 3, and 15). Duplex sonography of the extracranial vessels was carried out in all patients.

In addition to standard laboratory investigations, the following tests were performed: immunoglobulins G, M, and A; C-reactive protein; Waaler-Rose test; rheumatoid factor; serum β2-microglobulin; antinuclear antibodies; complement factors 3 and 4; cryoglobulins; cold agglutinins; lupus anticoagulant factor; anticardiolipin antibodies; syphilis and hepatitis serology; antistreptolysin titer; creatinine clearance; and urinary β2-microglobulin.

Results

Neurological Symptoms and Signs

Headache was the most frequent symptom in 14 patients, and vertigo was noted in eight (Table 1). Headache was frequently described as dull and diffuse and preceded focal neurological symptoms for 2 months to 15 years. Headache was not related to elevated blood pressure. Vertigo was reported 1–14 years before manifestation of focal symptoms in four patients and occurred simultaneously with stroke in the remaining four. Transient ischemic attacks were reported by 15 patients and occurred over 1–10 years, with a frequency of one attack per week to one per year. The most frequent symptoms were hemiparesis, sensory disturbances, and aphasia; dysarthria, visual field deficits, and drop attacks were reported less frequently. Completed stroke occurred in eight patients, with multifocal signs in two. Most symptoms were related to infarcts of the middle cerebral artery (MCA) territory. Seizures were ob-
TABLE 1. Neurological Symptoms and Signs in 17 Patients With Sneddon's Syndrome

<table>
<thead>
<tr>
<th>Patient/sex/age (years)</th>
<th>Nonspecific symptoms</th>
<th>Focal symptoms</th>
<th>Present status</th>
<th>Organic brain syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Stroke: left hemiparesis and hemihyphesthesia, recurrent TIAs with drop attacks</td>
<td>Focal signs</td>
<td></td>
</tr>
<tr>
<td>1/F/40</td>
<td>H,V</td>
<td></td>
<td>Left hemiparesis and hemihyphesthesia</td>
<td>Moderate</td>
</tr>
<tr>
<td>2/F/37</td>
<td>H,V</td>
<td>TIA with left arm paresthesia</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>3/M/40</td>
<td>V</td>
<td>Multiple strokes with right hemiparesis, hemianopia, and global aphasia; left hemiparesis</td>
<td>Mixed aphasia, apraxia, right hemianopia, tetraparesis, pseudobulbar palsy, developmental reflexes</td>
<td>Severe</td>
</tr>
<tr>
<td>4/F/63</td>
<td>H</td>
<td>TIA with aphasia; Jacksonian fits and grand mal</td>
<td>No</td>
<td>Slight</td>
</tr>
<tr>
<td>5/M/48</td>
<td>No</td>
<td>Stroke with aphasia and right hemiparesis, paresthesia, and hemiparesis</td>
<td>Amnestic aphasia, right hemiparesis and hemihyphesthesia</td>
<td>Slight</td>
</tr>
<tr>
<td>6/F/34</td>
<td>H,V</td>
<td>Recurrent TIAs with aphasia, right hemiparesis, left hemiparesis and hemihyphesthesia</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>7/F/33</td>
<td>H,V</td>
<td>Recurrent TIAs with left hemiparesis and drop attacks</td>
<td>No</td>
<td>Slight</td>
</tr>
<tr>
<td>8/F/41</td>
<td>H</td>
<td>TIA with left hemihyphesthesia</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>9/F/35</td>
<td>H,V</td>
<td>Recurrent TIAs with left hemiparesis and left arm paresthesia</td>
<td>Primitive motor patterns</td>
<td>Moderate</td>
</tr>
<tr>
<td>10/F/46</td>
<td>H,V</td>
<td>Stroke with left facial and arm palsy; Recurrent TIAs with left hemiparesis, hemihyphesthesia, right hemianopia, and dysarthria; Jacksonian fit</td>
<td>Left hemiparesis and hemihyphesthesia</td>
<td>Moderate</td>
</tr>
<tr>
<td>11/F/33</td>
<td>H</td>
<td>Stroke with right arm paresis; Recurrent TIAs with left arm paresthesia and left hemianopia</td>
<td>Right hemiparesis</td>
<td>Slight</td>
</tr>
<tr>
<td>12/F/31</td>
<td>H</td>
<td>Stroke with right hemiparesis; Recurrent TIAs with right hemihyphesthesia and hemiparesis</td>
<td>Right hemiparesis</td>
<td>Slight</td>
</tr>
<tr>
<td>13/F/31</td>
<td>H</td>
<td>TIA with left arm paresthesia and amaurosis fugax</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>14/F/54</td>
<td>H,V</td>
<td>Recurrent TIAs with right hemiparesis, expressive aphasia, left and right hemihyphesthesia, and double vision</td>
<td>Primitive motor patterns</td>
<td>Moderate</td>
</tr>
<tr>
<td>15/F/43</td>
<td>No</td>
<td>Stroke with right hemiparesis and hemihyphesthesia</td>
<td>Mixed aphasia, right hemiparesis and hemihyphesthesia, pseudobulbar dysarthria</td>
<td>Slight</td>
</tr>
<tr>
<td>16/F/27</td>
<td>H</td>
<td>TIA with left paresthesia and hemianopia</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>17/F/51</td>
<td>H</td>
<td>Stroke with left hemiparesis</td>
<td>Left hemiparesis</td>
<td>No</td>
</tr>
</tbody>
</table>

H, headache; V, vertigo; TIA, transient ischemic attack.

served in four patients, and three had previous ischemic attacks. On clinical examination at the time of this study, one patient was demented and required permanent nursing care. Eight patients showed advanced neurological impairment but lived on their own. In addition to progressive cognitive impairment, eight patients had hemiparesis, three hemihyphesthesia, and three aphasia. The remaining eight patients had only minor deficits or had recovered from neurological disabilities. Mental deterioration with loss of concentration and memory deficits was reported in 11 of 17 patients, but only one had clinically apparent dementia with apraxic and aphasic deficiencies; he was unable to read and write. Moderately elevated blood pressure (160/100 to 210/120 mm Hg) was found in 10 of 17 patients without underlying hormonal or renal disease. Fundoscopy showed grades I–II hypertensive vascular changes in four of 10 patients. There was no correlation between hypertension and progression of SS.

CT and MR Findings

CT scans were abnormal in 12 of 16 patients, whereas MRI demonstrated abnormalities in 16 of 17 patients. On CT scan, supratentorial infarctions were seen in 10 of 16 patients, located in the territory of the MCA in eight, the anterior cerebral artery (ACA) in one, and the posterior cerebral artery (PCA) in another patient. Three cases had multiple infarcts. One patient, who had a rapid progression of dementia, had a multiplicity of lesions, including bilateral infarctions related to the
MCA and PCA territories on both CT scan and MRI (Figure 2, left panel). On CT scan, areas of focal hypodensities within the deep white matter were detected in four of 16 patients and cortical or subcortical atrophy in eight of 16.

The patient who was not examined by CT had deep white matter changes on MRI. In all other patients, MRI confirmed the CT findings and revealed additional deep white matter changes in 14 (Figure 3, left panel) and infratentorial lesions in eight (Figure 3, right panel). Deep white matter lesions were characterized by multiple periventricular hyperintense areas and infratentorial lesions by small bright foci in the cerebellar hemispheres. In addition, MRI showed more lesions in individual patients than did CT scans.

MRA of the intracranial vessels showed patent ICA and basilar artery, circle of Willis and proximal MCA, PCA, and ACA in 16 patients. One patient had multiple branch occlusions of the MCA, ACA, and PCA (Figure 2, right panel), which correlated with x-ray cerebral angiography. The two other angiograms were unremarkable. The extracranial arteries appeared normal on ultrasound in all cases.

**Dermatologic Signs and Skin Biopsy**

GLR was evident in all patients, predominantly located on the lower extremities, buttocks, and trunk. It appeared as a persisting discoloration with a reddish-purple reticulated pattern of irregular broken circles and often worsened during neurological deterioration as well as during pregnancy. On skin biopsy the involved vessels were small to medium-sized arteries at the border of dermis to subcutis, with a distinct histopathological time course. Early inflammatory reactions (Figure 4) were followed by subendothelial proliferation and a late fibrotic stage.

**Laboratory Findings**

Decreased creatinine clearance was seen in eight patients. Five patients had elevated erythrocyte sedimentation rates, and five showed elevated total cholesterol levels (250–350 mg/dL). The other parameters, including standard urinalysis, antiphospholipid antibodies, cold agglutinins, and cryoglobulins, were within normal range.

**Discussion**

The original definition of SS described a distinct entity characterized by GLR and stroke. However, the differentiation from phenomenologically similar disorders remains difficult. Research on treatment strategies requires more knowledge about the pathophysiology of SS and calls for more conclusive diagnostic criteria.

In this series there was a high incidence of prodromal signs such as headache (14 of 17; 82%) and vertigo (eight of 17; 47%). These symptoms preceded the onset of GLR and focal neurological symptoms by several years. Although these signs are nonspecific, the high incidence suggests a causal rather than a coincidental relation.

Although SS represents a chronic relapsing disease, the disease course varied markedly with years of stable disease or even partial remissions of neurological deficits. Only one patient developed disabling functional and intellectual impairment.
Neuroradiological confirmation of cerebral involvement is a key feature of the diagnosis of SS, especially in the presence of transient or nonspecific neurological symptoms. MRI demonstrated more lesions than CT scan. These lesions were often small and multifocal, located predominantly in the periventricular deep white matter; they were present in 14 patients (82%). Involvement of the vertebrobasilar system was detected only by MRI and was seen in nearly half of our patients (eight of 17; 47%). The MRI findings were not specific for SS, and similar features may be detected in lupus erythematosus or even multiple sclerosis. Therefore, MRI scans must be interpreted in conjunction with clinical features. Patient 8, with GLR, histological evidence of SS, and a transient ischemic attack, had a normal magnetic resonance examination. Thus, a positive MRI can support the diagnosis of SS, but a negative result cannot exclude cerebral involvement. Although sequential MRI studies are necessary to monitor the progression of the disease, the baseline MRI was the primary method for confirming brain involvement in SS.

MRA was sufficient to demonstrate the patency of the proximal ACA, MCA, and PCA. In this series MRA revealed abnormalities in one patient who had multiple occlusions of MCA and ACA branches, which correlated with x-ray angiography. Involvement of larger arteries is a rare finding in SS, and this patient has been discussed previously. The extracranial carotid and vertebral arteries appeared normal on duplex scans in all our patients. Many previous reports of x-ray angiography in SS have not shown substantial abnormalities, whereas others demonstrated occlusions in distal branches. Because SS affects predominantly small intracranial arteries and x-ray angiography carries some risks, we suggest the combination of MRA and duplex sonography as a strategy for exclusion of large-vessel obstruction. However, the negative predictive value of MRA for intracranial vascular disease remains to be established.

Laboratory investigations were of limited diagnostic importance in our patients but remain mandatory for differential diagnosis. Decreased creatinine clearance in 47% (eight of 17) of our patients suggest kidney involvement, and data from previously published cases provide evidence for manifestation of SS outside skin and brain. None of our patients had antiphospholipid antibodies, a finding that is in agreement with previous studies.

At present no final conclusion about the pathophysiology of cerebral involvement is possible. Skin biopsies and previous data suggest that the intracranial vessels may be affected by a process that follows the histopathological changes seen in skin arteries. Stage-related differences may explain contradictory reports on the therapeutic effect of steroids and azathioprine.

None of the dermatological, neurological, or neuroradiological findings are diagnostic for SS. A large number of diseases that can occur with GLR (such as polyarteritis nodosa, systemic lupus erythematosus, cryoglobulinemia, livedoid vasculitis, antiphospholipid antibody syndrome, cold agglutinin disease, arteriosclerosis, and others) must be excluded by the appropriate clinical and laboratory tests. Diagnostic difficulties may arise when no other pathological signs except GLR are found. This clinical condition, known as “idiopathic GLR,” may not exist as a separate entity but may represent a very early stage of SS.

Histological findings were characteristic and appeared to be reliable for diagnosis in our patients. Substantial information to confirm cerebral involvement was derived from MRI. However, neither the signal pattern nor the distribution of white matter lesions were
specific for SS. Similar findings may be seen in other cerebrovascular disorders affecting small arteries. The gamut of disorders that present with small bright foci on T2-weighted MRI is extremely large.46

In conclusion, we suggest the following diagnostic approach for SS: the main criteria are GLR with typical histopathological findings on skin biopsy and focal neurologic deficits. Supportive criteria are a history of transient ischemic attacks or stroke and evidence of small bright foci on T2-weighted MRI.

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