

# Sneddon's Syndrome: A Case Report

James Lahti, MD, MPH, Baltimore, Maryland

Thomas Yu, BS, Baltimore, Maryland

Joseph W. Burnett, MD, Baltimore, Maryland

Linda Lutz, MD, Baltimore, Maryland

Marian P. LaMonte, MD, MSN, Baltimore, Maryland

Ruwani Gunawardane, MD, Baltimore, Maryland

## GOAL

To learn how to recognize the characteristics of and treatments for Sneddon's syndrome

## OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Recognize the clinical presentation of Sneddon's syndrome.
2. Distinguish between Sneddon's syndrome and antiphospholipid antibody syndrome.
3. Outline the therapeutic options for Sneddon's syndrome.

**CME** Test on page 220.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: February 2001.

This activity has been planned and implemented in accordance with the Essentials and Standards of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Albert Einstein College of Medicine and Quadrant HealthCom, Inc. The Albert Einstein College of Medicine is accredited by the

ACCME to provide continuing medical education for physicians.

Albert Einstein College of Medicine designates this educational activity for a maximum of 1.0 hour in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

This activity has been planned and produced in accordance with ACCME Essentials.

*We report a case of Sneddon's syndrome with the triad of livedo reticularis, hypertension, and neurologic symptoms. The procedures for diagnosis and the tests to delineate clotting abnormalities are examined.*

Drs. Lahti, Burnett, and Lutz and Mr. Yu are from the Department of Dermatology, and Drs. LaMonte and Gunawardane are from the Department of Neurology, all at the University of Maryland School of Medicine, Baltimore. Dr. Lahti was a Dermatology Resident.

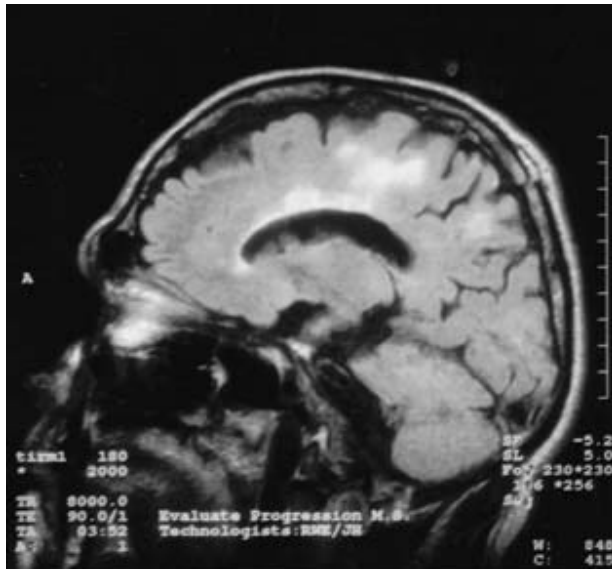
Mr. Yu was a medical student. Dr. Burnett is a Professor of Dermatology. Dr. Lutz is an Assistant Professor of Dermatology. Dr. LaMonte is an Assistant Professor. Dr. Gunawardane is Associate Professor of Neurology.

Reprints: Joseph W. Burnett, MD, Department of Dermatology, University of Maryland School of Medicine, 405 W Redwood St, 6th Floor, Baltimore, MD 21201.

**S**neddon's syndrome (SS) is an infrequent neurocutaneous disorder characterized by the triad of generalized livedo reticularis, hypertension, and neurologic symptoms. The neurologic symptoms are many and include transient ischemic attacks, strokes, and dementia. The syndrome was first described in 1907<sup>1</sup> and later recognized as a separate entity in 1965.<sup>2</sup> We describe the case of a 42-year-old man with SS presenting with livedo reticularis, hypertension, and cerebrovascular involvement.

## Case Report

A 42-year-old Caucasian male presented for evaluation of progressive neurologic deterioration. Except for hypertension, he was in normal health until 1987 when he began to have episodic weakness on the left



**Figure 1.** Sagittal magnetic resonance image showing multiple infarcts (pale regions) in the gray matter.

side of his face, arm, and leg, with associated numbness. A magnetic resonance image (MRI) and computed tomography scan were performed, and results were normal. A year later, he developed vertigo. In 1993, the patient noticed a reticular-patterned livedo involving his posterior trunk, lower legs, and wrists. Shortly thereafter, he experienced 2 cerebrovascular accidents with numbness and weakness of his left face, left leg, and both arms. He also began to notice impaired memory, personality changes, and light-headedness. An MRI was performed, which revealed multiple small infarcts (Figure 1).

On examination, the patient was able to converse even though he had dysarthric speech. His skin was warm and moist but had a generalized livedo reticularis that was more pronounced on his buttocks and back (Figure 2). His peripheral pulses were good, and he had good capillary refill. There were no cardiac murmurs or bruits over the carotid arteries. Neurologically, the patient had an apathetic expression, slow cognition, a depressed mood, and a diminished vocabulary. He had mild apraxia that was greater on the left side than on the right. The cranial nerves were intact, except for abnormal saccades to the left, a small decrease in facial expression, and a slight deviation of the tongue to the right. He had full motor strength except for his left hand, which had a pronator drift, and diminished fine motor skills. His sensation was reduced on the right side of his body. The patient's gait was normal, although slow. The rest of the examination was unremarkable.

The following laboratory studies were normal: serum cryoglobulins; antibodies for lupus anticoagulant, cardiolipin, antinuclear, anti-Ro (Sjögren's



**Figure 2.** Patient at presentation demonstrating livedo reticularis.

syndrome A) and anti-La (Sjögren's syndrome B); rheumatoid factor; homocysteine, folate, or B<sub>12</sub> levels; sedimentation rate; cholesterol; and triglycerides. A cerebral angiogram revealed multiple small intracranial arteries, with long segmental areas of narrowing and gradual occlusion. The larger cerebral vessels were normal. An echocardiogram and a renal ultrasound examination were normal. Two 4-mm punch biopsies were performed on involved and uninvolved skin of his back. Only nonspecific histology without evidence of vasculitis was detected.

Because the patient had progressive neurologic deterioration on aspirin, he was anticoagulated with warfarin. His international normalized ratio has been maintained between 2.5 and 3.5. After 12 months of therapy, he has remained free of progression of his neurologic symptoms but has only partial resolution of his cutaneous lesions.

### Comment

An estimated 4 new cases of SS occur per million inhabitants per year.<sup>3</sup> The syndrome is clinically defined as a triad of generalized livedo reticularis, hypertension, and neurologic symptoms. In 1965, Sneddon described 6 young patients with livedo reticularis who experienced strokes.<sup>2</sup> A female predominance was later confirmed.<sup>3,4</sup> Other features of SS include onset of the disease in the third or fourth decade, arterial

hypertension, history of fetal loss, and Raynaud's phenomenon.<sup>5</sup> Attempts have been made to subclassify SS into primary and secondary—primary SS is diagnosed if no underlying etiologic condition can be identified, and secondary SS is diagnosed if an etiologic condition is identified.<sup>4</sup> The timing of the cutaneous and central nervous system findings can be variable, with 75% of patients having livedo reticularis preceding central nervous system involvement by several years.<sup>4</sup> The diagnosis of SS is made by clinical features because biopsies and serologies are often nonspecific.<sup>4,6,7</sup> The etiology is thought to be a partial to complete occlusion of small- to medium-sized arteries possibly due to an autoimmune disorder or thrombophilic state.<sup>4</sup> A 1- to 2-cm biopsy from seemingly normal skin in the center of livedoid skin has been reported to have an 80% yield in finding characteristic histopathologic changes.<sup>8</sup> These consist of inflammatory changes in the endothelium in the early stages, followed by subendothelial myointimal hyperplasia, with partial and complete occlusion of the involved arterioles.<sup>4,8</sup> These findings, however, have not been replicated in other studies.<sup>4,9</sup> The lack of pathologic changes in the present case is consistent with the findings in the later studies.

Vascular changes in SS are systemic and not limited to the skin. Angiographic findings in this patient consisted of multiple small intracranial arteries with areas of narrowing and occlusion with normal larger vessels. Because the small cortical arteries are predominantly affected in SS, MRI and conventional angiography may fail to reveal any abnormalities.<sup>10</sup> A reported case of a brain biopsy in SS also failed to reveal any evidence of vasculitis.<sup>11</sup> Some authors have advocated using computer blood flow scintigraphy to detect abnormalities.<sup>10</sup>

There is considerable confusion between the diagnosis of SS and antiphospholipid antibody syndrome (APS) because the clinical features of SS and APS are similar.<sup>12-16</sup> Both diseases are systemic, with common features that include livedo reticularis, neurologic involvement, hypertension, and fetal loss.<sup>4,17</sup> The classification of APS requires vascular thrombosis or pregnancy loss in association with either the anticardiolipin or lupus anticoagulant antiphospholipid protein antibodies (APAs).<sup>18</sup> Like SS, the first clinical signs of APS may be cutaneous.<sup>12</sup> The pathologic findings of SS and APS are also similar.<sup>14</sup> Like SS, APS also has been subclassified into primary and secondary syndromes. Primary APS occurs when a patient does not have an underlying systemic disorder; secondary APS occurs where there is associated underlying disease, most commonly systemic lupus erythematosus (SLE).<sup>19,20</sup> APAs have been reported in SS, though the prevalence varies widely.<sup>9,14,15</sup> Whereas

some authors have refused to diagnose SS when APAs were present,<sup>3</sup> others have not.<sup>14</sup> Also, though the diagnosis of SS is usually excluded in patients with SLE, some feel that there may be a continuum among SS, primary APS, and SLE.<sup>14</sup>

The underlying mechanism behind SS and APS is thrombosis. It has been hypothesized that APAs interfere with the kinetics of coagulation reactions or stimulate the prothrombotic activities of endothelial cells or monocytes and promote coagulation.<sup>19,21</sup> Patients with clinical manifestations of APS may have negative assays for lupus anticoagulant and anticardiolipin antibody, yet may have antibodies against other phospholipids. These include the presence of circulating anti- $\beta_2$ -glycoprotein-I antibodies, low-positive titers of IgG or IgM anticardiolipin antibodies, IgA isotype of anticardiolipin, and antibodies to other phospholipids or phospholipid-binding proteins. These elements require further standardization before they can be included as formal criteria of APS.<sup>18</sup> Other APAs associated with thrombosis and cerebrovascular events include antiphosphatidylserine, antiphosphatidylinositol, and antiphosphatidylethanolamine.<sup>22,23</sup> Cofactors and antigenic targets identified in APS include prothrombin, coagulation factor V, protein C, protein S, thrombomodulin, annexin V, heparitin sulfate, heparitin sulfate proteoglycans, prostacyclin production, and kininogens.<sup>19,23,24</sup>

There are no large studies of therapy in SS. Because of its clinical similarity to APS, therapy for the latter entity is extrapolated to the former syndrome. The goal of therapy is to prevent thrombotic complications, particularly those of the central nervous system; consequently, there are more data on the management of thrombosis in APS. In addition, it is suggested that antiplatelet therapy alone is not effective in patients with APA.<sup>14</sup> Long-term anticoagulation therapy with the international normalized ratio maintained at or above 3 is advised.<sup>25,26</sup> Other therapies used in severe APS include corticosteroids, cyclophosphamide, intravenous gammaglobulins, and plasmapheresis.<sup>20</sup> Currently, the mainstay of therapy for SS is warfarin, a drug that does not guarantee the prevention of thrombotic complications.<sup>25,27</sup> The use of corticosteroid and immunosuppressive agents without anticoagulation appears to be without benefit and may be harmful.<sup>3,14</sup> Even though the patient was taking aspirin before presentation, he had experienced a progression of symptoms. After diagnosis, he has had a stable course with the use of warfarin anticoagulation therapy.

In summary, this case of SS illustrates that this disease can be diagnosed clinically but whose pathology on biopsy is often nonspecific.

The systemic nature of the thrombotic process— as well as some of the proposed etiologies—was discussed. The therapeutic aim is to prevent thrombotic complications, which is best achieved with warfarin anticoagulation therapy.

## REFERENCES

- Ehrmann S. Ein neues gefasssymptom bei lues. *Wein Med Wochenschr.* 1907;57:777-782.
- Sneddon IB. Cerebrovascular lesions and livedo reticularis. *Br J Dermatol.* 1965;77:180-185.
- Zelger B, Sepp N, Stockhammer G, et al. Sneddon's syndrome: a long-term follow-up of 21 patients. *Arch Dermatol.* 1993;129:437-447.
- Schellong SM, Weissenborn K, Niedermeyer J, et al. Classification of Sneddon's syndrome. *Vasa.* 1997;26:215-221.
- Lubach D, Schwabe C, Weissenborn K, et al. Livedo racemosa generalisata: an evaluation of 34 cases. *J Am Acad Dermatol.* 1990;22:633-639.
- Rebello M, Val JV, Carijo F, et al. Livedo reticularis and cerebrovascular lesions (Sneddon's syndrome)—clinical, radiological, and pathological features in eight cases. *Brain.* 1983;106:965-979.
- Stevens WP, Ferguson LT. Livedo reticularis and cerebrovascular disease. *Postgrad Med J.* 1982;58:70-73.
- Zelger B, Sepp N, Schmid KW, et al. Life history of cutaneous vascular lesions in Sneddon's syndrome. *Hum Pathol.* 1992;23:668-675.
- Fetoni V, Berti E, Cecca E, et al. Sneddon's syndrome: clinical and immunohistochemical findings. *Clin Neurol Neurosurg.* 1994;96:310-313.
- Sumi Y, Ozaki Y, Itoh S, et al. Cerebral blood flow-SPECT in a patient with Sneddon's syndrome. *Ann Nucl Med.* 1999;13:109-112.
- Geschwind DH, FitzPatrick M, Mischel PS, et al. Sneddon's syndrome is a thrombotic vasculopathy: neuropathologic and neuroradiologic evidence. *Neurology.* 1995;45:557-560.
- Gibson GE, Su D, Pittelkow D. Antiphospholipid syndrome and the skin. *J Am Acad Dermatol.* 1997;36:970-982.
- Gantcheva M, Tsankov N. Livedo reticularis and cerebrovascular accidents (Sneddon's syndrome) as a clinical expression of antiphospholipid syndrome. *J Eur Acad Dermatol Venereol.* 1999;12:157-160.
- Frances C, Papo T, Wechsler B, et al. Sneddon syndrome with or without antiphospholipid antibodies: a comparative study in 46 patients. *Medicine (Baltimore).* 1999;78:209-219.
- Kalashnikova LA, Korczyn AD, Shavit S, et al. Antibodies to prothrombin in patients with Sneddon's syndrome. *Neurology.* 1999;53:223-225.
- Kalashnikova LA, Nasonov EL, Kushenbaeva AE, et al. Anticardiolipin antibodies in Sneddon's syndrome. *Neurology.* 1990;40:464-467.
- Piette JC, Cacoub P, Wechsler B. Renal manifestations of the antiphospholipid syndrome. *Semin Arthritis Rheum.* 1994;23:357-366.
- Wilson WE, Gharavi AE, Koike T, et al. International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome. *Arthritis Rheum.* 1999;42:1309-1311.
- Nahass GT. Antiphospholipid antibodies and the antiphospholipid antibody syndrome. *J Am Acad Dermatol.* 1997;36:149-168.
- Asherson RA, Cervera R, Piette JC, et al. Catastrophic antiphospholipid syndrome. *Medicine.* 1998;77:195-207.
- Amigo MC, Garcia-Torres R, Robles M, et al. Renal involvement in primary antiphospholipid syndrome. *J Rheumatol.* 1992;19:1181-1185.
- Tuhim S, Rand JH, Godbold JH, et al. Elevated antiphosphatidyl serine antibodies are a risk factor for ischemic stroke [abstract]. *Neurology.* 1998;50:A246.
- Tanne D, Triplett DA, Levine SR. Antiphospholipid-protein antibodies and ischemic stroke. *Stroke.* 1998;29:1755-1758.
- Rand JH. Antiphospholipid antibody syndrome: new insights on thrombogenic mechanisms. *Am J Med Sci.* 1998;316:142-151.
- Khamashta MA, Cuadrado MD, Mujic F, et al. The management of thrombosis in the antiphospholipid-antibody syndrome. *N Engl J Med.* 1995;332:993-997.
- Kearon C, Gent M, Hirsch J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. *N Engl J Med.* 1999;340:901-907.
- O'Riordan JI, Javed M, Murphy R, et al. Sneddon's syndrome—clinical course and out-come. *Ir Med J.* 1995;88:66-67.

### DISCLAIMER

The opinions expressed herein are those of the authors and do not necessarily represent the views of the sponsor or its publisher. Please review complete prescribing information of specific drugs or combination of drugs, including indications, contraindications, warnings, and adverse effects before administering pharmacologic therapy to patients.

### FACULTY DISCLOSURE

The Faculty Disclosure Policy of the College of Medicine requires that faculty participating in a CME activity disclose to the audience any relationship with a pharmaceutical or equipment company that might pose a potential, apparent, or real conflict of interest with regard to their contribution to the program. It is required by the Accreditation Council for Continuing Medical Education that each author of a CME article disclose to the participants any discussion of an unlabeled use of a commercial product or device or an investigational use not yet approved by the Food and Drug Administration. Drs. Lahti, Burnett, Lutz, and LaMonte and Mr. Yu report no conflict of interest. At the time of publication, Dr. Gunawardane has not responded to requests for disclosure. Dr. Fisher reports no conflict of interest.