*Review Article*

# Sneddon Syndrome: A Comprehensive Overview

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Sneddon syndrome (SS) is an episodic or chronic, slowly progressive disorder and characterized by generalized livedo racemosa (patchy, violaceous, skin discoloration) and recurrent cerebrovascular events. The histopathology of skin and brain is remarkable for a noninflammatory thrombotic vasculopathy involving medium- and small-sized dermal and cerebral arteries, respectively. Approximately 80% of the SS patients are women with a median age of diagnosis at 40 years. However, the onset of the disease during childhood have been reported. Etiopathogenesis of SS is unknown with 2 primary mechanisms proposed – autoimmune/inflammatory versus thrombophilia. SS is primarily classified as antiphospholipid positive or negative type. Neurological manifestations usually occur in 3 phases: (1) prodromal symptoms such as headaches, dizziness, and vertigo, (2) recurrent strokes, and (3) early onset dementia. Livedo racemosa precedes the onset of recurrent strokes by more than 10 years, but in many instances, the significance of the skin lesion is recognized only after the appearance of the stroke. The involvement of the heart valves, systolic labile hypertension, and retinal changes are also commonly associated with this syndrome. Treatment of SS is primarily based on anecdotal reports. Antiplatelet and antithrombotic agents are used for secondary stroke prophylaxis, and a recent study showed a relatively lower stroke recurrence rate with the universal use of antiplatelet/antithrombotic agents. Routine use of anti-inflammatory or immunosuppressive therapies is controversial. Neuropsychiatric prognosis of SS is relatively poor with predominant deficits in the concentration, attention, visual perception, and visuospatial skills.

**Key Words:** Sneddon syndrome—livedo racemosa—ischemic strokes—dementia—antiphospholipid antibodies—thrombophilia



## Introduction

Sneddon syndrome (SS) is a rare, episodic or chronic, slowly progressive neurocutaneous syndrome and characterized by generalized livedo racemosa (LR; patchy, violaceous, skin discoloration) and recurrent cerebrovascular events. Ehrmann first reported the findings of LR in 1907 in a patient with syphilis. He described this as a blue slender tree-branching and "forked lighting" pattern that worsens in cool temperature.[1] Isolated cases of livedo and strokes have been described since 1959.[2,3] However, Dr. Ian Bruce Sneddon, a British dermatologist, first described a detailed analysis of 6 patients with generalized LR and recurrent strokes in 1965.[4] These patients did not have any evidence of systemic disorder such as systemic lupus erythematosus (SLE), polyarteritis nodosa, or syphilis. But, the term, Sneddon or SS, was not commonly used until the late 1970s.[5]

SS is a rare syndrome, and most publications involved a single case report or a small case series, with an only a rare report of a cohort consisting of >50 patients from a single institute.[6] Zelger et al estimated the incidence of SS as 4 new cases/year/1 million people, based on the diagnosis of 21 SS patients over 10 years in Innsbruck,

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Austria (Approximate population of 500,000 at the time of the study).[7] Rebello reported an SS prevalence of 0.26% in a hospital-based cohort of strokes from all causes.[8,9] Approximately 80% of the SS patients are women with a median age of diagnosis at 40 years. However, the onset of the disease during childhood have been reported. Furthermore, some patients with the presumed adult-onset disease have subtle symptoms and signs since early childhood period. Kume et al reported 1 Japanese SS patient, who started to have facial erythema and frostbite of the extremities from age 1 year and was ultimately diagnosed with SS at age 24 years.[10] Charles et al reported a girl child with SS who had excessive sleepiness, mood swings, and memory disturbance secondary to bilateral thalamic infarction.[11] Presentation of this rare disorder during the pediatric age group is discussed in details in a separate section.

## Classification

SS is primarily classified as antiphospholipid (aPL) positive or negative depending on the presence or absence of any of these 3 antibodies: anticardiolipin, lupus anticoagulant, and anti-beta 2-glycoprotein I.[12,13] Less than half of the patients with SS have positive aPL antibody.[14] Levine et al reported a 44-year-old SS patient with aPL positivity in 1988 and supported an idea of antibody-mediated pathogenesis.[15]

The aPL positive SS patients may behave like primary aPL antibody syndrome, which is characterized by secondary thrombophilia, recurrent fetal loss, and complications related to recurrent thrombosis.

Schellong et al proposed another classification method to distinguish different SS types: primary SS, that is, without any obvious etiologic factor and secondary SS in the presence of coexistent autoimmune disease or thrombophilia.[16]

## Clinical Features

SS is characterized by the association of typical skin lesion with recurrent strokes.

### *Dermatologic Manifestation*

The characteristic skin lesion is a patchy, net-like, violaceous skin discoloration known as LR. In American literature, the term livedo reticularis has been used often to describe lesion consistent with LR.[17] There is a debate in the literature about the nomenclature of racemosa (usually used in European papers) versus reticularis (usually used in US papers). It is important to note that the Sneddon's original paper used reticularis to describe the skin lesion and the distinction between these is a new concept and not distinguishable in older literature. However, reticularis lesions primarily occur due to a transient systemic problem such as cold exposure, causing a decreased dermal blood flow to produce a complete circular discolored ring. In young children, benign reticularis lesions have been reported as cutis marmorata. On the other hand, LR develops due to a permanent focal arteriolar obstruction which produces branching net-like pattern and broken circles-hallmarks of racemosa lesion (Fig 1). LR develops secondary to central arteriolar obstruction. As a dermal arteriole supplies a circular segment of a dermis, a circular pattern of low blood flow and hypoxia occur with maximum intensity along the periphery of that circle with reactive venular dilation, leading to the generation of a violaceous ring. This usually precedes the onset of recurrent strokes by more than 10 years.[7] However, less than half of the patients seek treatment for LR, and this can remain undiagnosed for more than 10-20 years. In many instances, the significance of LR is recognized only after the appearance of the stroke. LR usually first appears on the lower back and buttock. Slow progression is seen to involve dorsal aspects of the arms and thighs. Face, hands, and feet are only rarely involved. These lesions are painless and generally not associated with ulceration or edema. The severity of LR is not associated with the severity of the neurologic manifestation. Atypical centripetal progression was only rarely reported, with smaller, painful lesions spreading from hands and ankles with potential for the development of ulcers. Skin discoloration of LR remains uncharged to warming in contrast to livedo reticularis. However, episodic fluctuations of LR are noted with worsening in exposure to a cooler ambient temperature such as in winters. The LR is most prominent during the childbearing years with gradual improvement after the menopause. Intensification of the lesion has been reported during acute worsening of neurological symptoms.

Several other dermatological manifestations are seen in SS such as acrocyanosis, Raynaud's phenomenon, angiomatosis, circumscribed skin ulcer, annular atrophic lichen planus, and peripheral gangrene.[18-20] Some other skin findings such as skin erythema, localized scleroderma, etc are also reported; however, rather than a feature of SS, these may represent findings of other coexistent autoimmune diseases.

### *Neurological Manifestations*

Neurological manifestations usually occur in 3 phases.[7] In the first phase, prodromal symptoms such as headaches, dizziness, and vertigo predominate. This phase may even precede the appearance of LR. During the second phase, patients suffer from recurrent episodes of transient ischemic attacks (TIAs) and completed strokes. The nonspecific symptoms of the first phase may persist during the second phase. During the third phase, prominent cognitive decline and early onset dementia occur.

### *Headaches*

Headaches during the prodromal phase may mimic tension headaches or migraines and very rarely hemicranias continua.[21-24] Headaches are not related to systemic

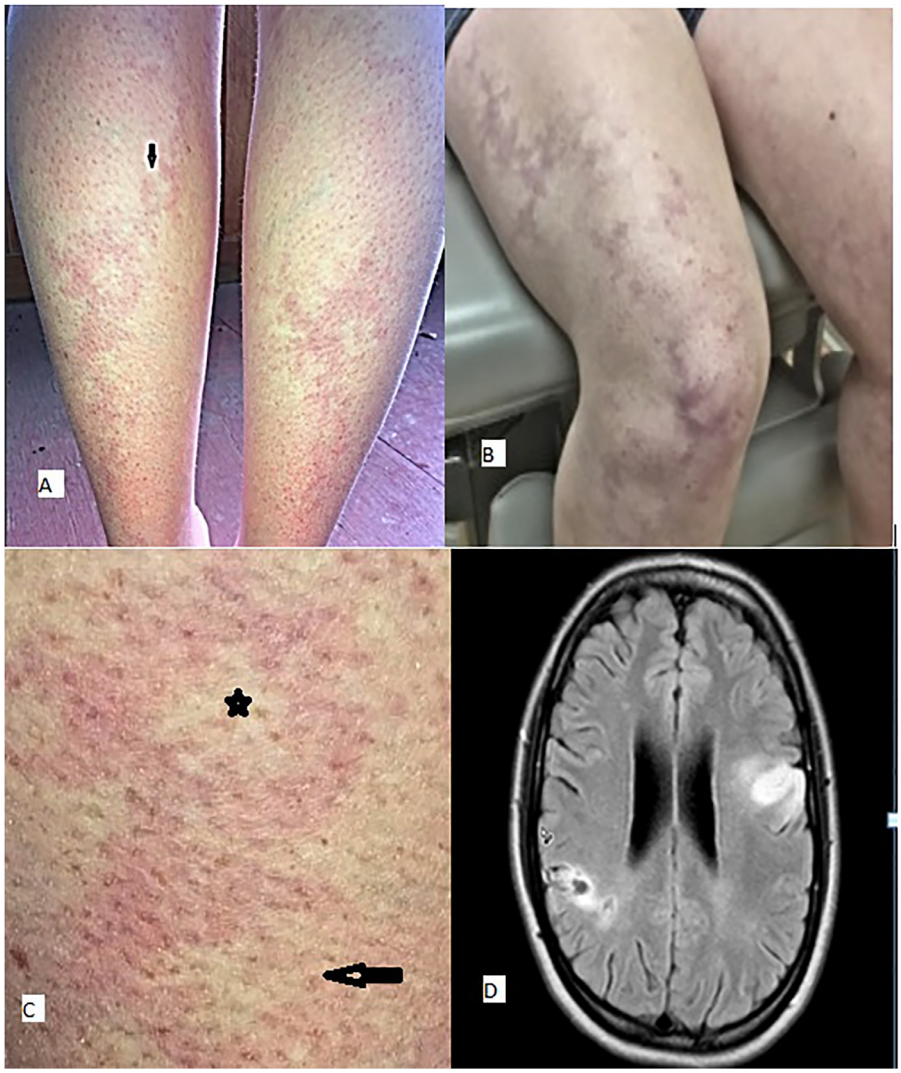


**Figure 1.** *(A and B). Livedo racemosa. An erythematous tree branching and forked-lightning pattern on the lower extremities. Please note the broken circle (arrow) pattern. (C). Close up view of the complete (note star inside the center of the lesion) and broken circles (arrow) of livedo racemosa. (D). FLAIR MRI brain image shows bilateral cortical infarctions.*

hypertension and mostly precede the onset of hypertension. There is no difference in the incidence of headaches between groups with or without hypertension and with or without the presence of aPL antibody.

### *Ischemic Strokes*

Recurrent episodes of focal neurological deficit occur during the second phase. Sensorimotor symptoms are the most common presenting feature of TIAs or strokes due to the predominant involvement of superficial and/or deep branches of the middle cerebral artery.[6] Visual impairment or aphasia is the second most common presentation. However, strokes in the territory of a posterior cerebral artery or posterior inferior cerebellar artery frequently remain clinically silent. Rapid clinical deterioration, due to recurrent strokes, is extremely rare soon after the first presentation. Tourbah et al reported 26 French patients (20 female) with SS. TIAs or strokes occurred at the age range of 22-58 years. LR preceded neurological symptoms in all the cases, by 15 years on average.[25] Acute hemiparesis was the most common focal neurological deficit, followed by aphasia and visual defect. Sensory symptoms and cerebellar signs were relatively infrequent.

### *Hemorrhagic Stroke*

Rare primary hemorrhagic strokes are reported – intracranial hemorrhage, intraventricular hemorrhage, diffuse subarachnoid hemorrhage, and subdural hematoma.[26,27] The hemorrhagic event can be due to rupture of collateral vessels, developing secondary to stenosis/occlusion of primary cerebral arteries. Secondary hemorrhage can also occur during treatment with an antiplatelet/antithrombotic agent.

*Early Dementia and Psychiatric Symptoms*

During the third phase, a prominent cognitive decline is seen and described in detail in the prognosis section.[28] However, cases of dementia from subclinical recurrent strokes have been reported without preceding episodes of focal neurological deficits.[29,30] Psychotic symptoms and suicidal attempts have also been reported.[10,31] Late-onset psychiatric symptoms without any relevant personal or family history or associated delusion in an SS patient may point to the diagnosis of SS-related psychosis rather than a primary psychotic disorder. These patients respond to a low dose of antipsychotics. Rarely neurological manifestation can precede LR. A young woman with SS was presented with a chronic visuospatial deficit in association with bilateral parietal hypoperfusion in a single-photon emission computerized tomography scan. Her brain MRI was normal at that time; however, later she presented with LR and multifocal cerebral infarction.[32]

*Seizures and Movement Disorders*

Seizures have been reported in SS, mostly secondary to remote symptomatic cerebral infarction, but can be a presenting feature preceding strokes, especially in aPL positive patients.[14] Movement disorders are only rarely associated with SS. Other than chorea associated with aPL positive patients, tremor can be an initial neurologic presentation. A report described a 54-year-old woman with a 12-year history of low-frequency cerebellar tremor of the head, trunk, and leg.[33] Her tremors would appear with standing and persist during walking. She also had broad-based gait and cognitive deterioration. The peripheral nervous system is rarely involved in SS in the form of axonal neuropathy or small fiber neuropathy.[7]

*Cardiac Manifestation*

Other than dermatological and neurological manifestation, several other organ systems may be affected, including involvement of the heart valves.[6] Thickening of heart valves and/or Libman-Sacks endocarditis are the most common cardiac pathology in SS. Mitral and aortic valves are most commonly involved, with or without stenosis and/or regurgitation. Clinical symptoms depend on the severity of the stenosis or insufficiency. Ischemic heart disease including myocardial infarction and hypertensive heart disease have been reported.[34] Fiore et al reported an SS patient with progressive aortic insufficiency who successfully underwent aortic valve replacement.[35] However, perioperative care can be complicated due to the risk of thrombosis, coexistent hypertension, and reduced creatine clearance.

*Hypertension*

Systolic labile hypertension is present in a large majority of the patients.[7] This can be diagnosed incidentally during pregnancy. Occasional end organ damage such as cardiac disease or retinal changes is seen secondary to long-standing hypertension; however, after several years of hypertensive phase, spontaneous improvement can be noted with the maintenance of normotension without antihypertensives in a sizable number of patients.

*Ophthalmological and Primary Vascular Manifestations*

Optic disc macroaneurysm, macular edema with hard exudates, delayed perfusion and obstruction of branch retinal artery, and retinal vein occlusion have been reported in SS. Retinal arteriovenous shunts, retinal vascular proliferation, petechial bleeding, and hypertensive vascular changes can also be seen.[36-39]Extracerebral arterial and venous thrombosis are reported such as digital artery thrombosis, superior mesenteric artery thrombosis, renal artery thrombosis, deep venous thrombosis, and pulmonary embolism.[6,40]

*Difference Between aPL Positive and Negative Patients*

The clinical features of aPL positive and negative patients have been compared. Most of the features are similar between these 2 groups, including the age of disease onset, gender distribution with female predominance, and the prevalence of LR as well as cardiac pathology.[14] However, aPL positive patients have a higher risk of thrombocytopenia, seizures, and chorea. In contrast, aPL negative patients may have thicker (>1 cm) LR.[14] In the past, aPL positive patients were thought to have less frequent strokes, less prominent cerebral atrophy, and more mitral valve disease rather than aortic valvulopathy. However, later studies did not show these findings consistently, and a similar rate of valvular heart disease, as well as recurrent spontaneous abortions, is noted in both aPL positive and negative SS patients.

## Etiology/Pathogenesis

Etiology of the SS is unknown, and pathogenesis is unresolved with 2 primary mechanisms proposed – autoimmune/inflammatory versus thrombotic disease. A subset of familial cases had early onset inflammatory features akin to vasculitis – recurrent fevers and elevated inflammatory markers.[41-43] However, histopathological evidence of inflammation is rare, and in some cases may represent reactive inflammation secondary to vascular lumen obstruction. Controversy exists if SS is a homogeneous disease, with identical pathogenesis, or closely related, heterogeneous diseases with similar clinical features, but with different pathogenesis.

*Genetics*

The initial trigger or etiologic factor for the development of SS is unknown and may involve the interplay of different conditions such as genetic makeup, inflammation, thrombophilia, and an autoimmune process. However, during

ongoing pathogenesis, a predominant thrombotic process is seen. Some authors proposed that SS is an autosomal dominant disease with variable penetrance due to the occurrence of rare familial cases.[41-43] Some of these patients perhaps have a recently described autosomal recessive condition with a mutation in the cat eye syndrome region, candidate 1(*CECR1*), encoding Adenosine deaminase 2 (ADA2).[44] A genetic predisposition to endothelial dysfunction can be a primary factor with secondary development of thrombosis over the damaged endothelium.

### *Autoimmune Process*

An acquired autoimmune process might also induce similar endothelial damage and subsequent aggravated thrombotic process. The disproportionate occurrence of this disease in females, especially during the reproductive years, similar to some other autoimmune diseases such as systemic lupus erythematosus (SLE), is also intriguing. The exact molecular mechanism of this phenomenon has not been explored but may be related to the presence of 2 functional X chromosomes and an alteration in the cytokine level during pregnancy in females.

### *Pathogenesis of Predominant Neurocutaneous Manifestation*

It is also unclear why a neurocutaneous manifestation predominates in SS. One group of authors hypothesized that this is due to the common ectodermal origin of both skin and brain.[45] However, another group opined that this is a systemic dysfunction of the arterial bed, including arterial beds of the internal organs. But, the systemic pathology is not frequently confirmed due to a paucity of histopathological samples and the presence of a better compensatory mechanism in these organs.[46]

### *Pathogenesis of Stroke*

The pathogenesis of the LR has been described in the pathology section. Recurrent TIAs and strokes are likely due to in situ thrombosis of middle- and small-sized cerebral vessels, although there was an initial concern that embolization secondary to valvular diseases may be partially responsible for strokes. However, 1 recent study, with radiologic analysis of diffusion-weighted imaging during acute strokes, postulated that strokes are most likely not cardioembolic in origin.[6] Different topographic patterns of strokes (as described below) are also not dependent on the presence or absence of valvular heart disease – another indication that cardioembolism may not play a significant role in the causation of cerebral infarction.

### *Cardiac Pathogenesis*

The pathogenesis of heart valve dysfunction is also unknown. It has been hypothesized that immune complex deposition may produce valvular endothelial dysfunction with subsequent thrombus formation on the damaged valve. Several vascular risk factors such as hypertension, exposure to estrogen-containing contraceptives, and smoking have been investigated to determine their role in disease progression and stroke recurrence. Although avoidance of these risk factors are preferable and can lessen the risk of progression of the disease process, a definitive link between these risk factors and the disease progression has not been established.

## Evaluation

There is no specific biologic marker for the diagnosis of SS. The patients who initially present with only LR should undergo testing to rule out other etiologies of livedo (detailed in the Differential Diagnosis Section). The patients who present after an episode of stroke should undergo an extensive investigation including neuroimaging to rule out other causes of strokes in young adults, summarized in Table 1.

aPL antibodies are absent in aPL negative cases. However, inconsistently other thrombophilic conditions are present such as factor V Leiden, protein S deficiency, protein Z deficiency, etc.[47-52] Different relevant blood tests are summarized in Table 2.

### *Imaging*

Brain MRI is superior to CT scan for detection small infarctions, especially those located in the infratentorial

**Table 1.** *Differential diagnosis of ischemic strokes in young adults*

| Etiology | Examples |
|---|---|
| Cardiac | Congenital heart disease with or without previous surgery, endocarditis, cardiomyopathy, prosthetic heart valve, arrhythmias, and paradoxical embolism |
| Hematologic | Sickle cell disease, hyperviscosity, and inherited and acquired hypercoagulable stable |
| Vasculopathy | Focal cerebral arteriopathy, moyamoya, arterial dissection, vasculitis(primary or secondary form associated with collagen vascular disease), Sneddon syndrome, migraine, and reversible cerebral vasoconstriction syndrome |
| Metabolic/genetic disorders | CADASIL (cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy), Fabry disease, homocystinuria, and MELAS |
| Other causes | Substance abuse, postradiation, and trauma |

**Table 2.** *Laboratory tests in a suspected patient with Sneddon syndrome*

| | |
|---|---|
| Standard tests | Electrolytes, blood urea nitrogen, creatinine, glucose, calcium, and complete blood count |
| Vascular risk factors | HbA1c, total cholesterol, triglycerides, and proteinuria |
| Inflammatory markers | Erythrocyte sedimentation rate, C-reactive protein |
| Autoimmune/collagen vascular disease risk factor | Antinuclear antibodies, antinative DNA antibodies, and antineutrophilic cytoplasmic antibodies |
| Immune complex deposition risk | Complement consumption parameters C3, c4, and CH50 activity |
| Thrombophilia workup | Antiphospholipid antibodies, protein C, protein S, factor V Leiden, Prothrombin G20210A, methylenetetrahydrofolate reductase (MTHFR)mutations, and homocysteine levels |

region. However, CT scan can detect large-sized subacute or chronic territorial stroke as well as rare cases of acute intracranial hemorrhage. Diffusion-weighted imaging MRI is sensitive for the detection of acute stroke and susceptibility-weighted imaging is preferable to detect microbleed.

### Topographic Patterns of Cerebral Infarctions

Three different topographic patterns of cerebral infarctions are seen.[6] These are − (1) large territorial cortical-subcortical infarction due to an occlusion of a middle size artery; (2) distal, smaller size cortical-subcortical infarction secondary to involvement of a superficial, distal perforating artery; (Fig 1D) and (3) a rarer pattern of deep white matter infarction due to thrombosis of the deep perforating artery. This third pattern, radiologically similar to hypertensive lacunar infarction, can be seen in the absence of hypertension. Strokes can involve both supra- and infratentorial regions, but basal ganglia and cerebellar involvements are relatively rare in comparison to strokes that occur secondary to hypertension or cardioembolism.[53] Relatively large territorial infarction can be present but does not involve the whole arterial territory. Moderate supratentorial leukoencephalopathy is commonly present as well as diffuse cortical atrophy. The focal atrophic pattern due to a large infarction may superimpose on the diffuse atrophy.

### Other Imaging Studies Including Vascular and Metabolic Imaging

Ultrasound of the carotid artery can detect small atherosclerotic plaques in a small minority of the patients. However, other systemic vascular risk factors such as the history of smoking and hypertension are likely to contribute to the formation of the arterial plaque. Clinically silent micro embolisms have been noted by transcranial Doppler in 1 study; however, most patients likely have in situ thrombosis of cerebral blood vessel rather than arterio-arterial or cardioembolic embolism.[54] MR angiogram is usually normal due to its relatively low sensitivity in detecting small cerebral vessel vasculopathy. However, conventional angiogram typically shows stenosis and obstruction of distal cerebral arteries with the occasional presence of fine collaterals.[55] Rarely, prominent leptomeningeal and transdural anastomotic vessels can be formed spontaneously in an attempt to establish collateral circulation, similar to moyamoya syndrome. A review included 8 patients with various combinations of moyamoya, SS, and aPL antibodies. Most patients had a favorable response from antiplatelet or anticoagulant or steroid therapy. Besides expanding the spectrum of associations with moyamoya, the authors also suggested testing for aPL antibodies in idiopathic moyamoya based on this observation.[56] However, in contrast to moyamoya, the large arteries of the circle of Willis are not obstructed in most patients. These abnormal collateral vessels can rupture, causing intracranial hemorrhage. Echocardiography is very valuable to detect valve abnormalities in SS. Cardiac MRI can be useful to detect subendocardial scar and intramyocardial fibrosis due to microvascular coronary artery disease, without an obviously detectable abnormality in the coronary angiography.[57]

Rare reports of metabolic imaging are present. Juengling et al reported a woman with SS and dementia, who had generalized cortical and subcortical hypometabolism in the Fluorodeoxyglucose Positron Emission Tomography scan. Similarly, there are rare reports of single-photon emission computerized tomography showing accentuated diffuse hypoperfusion preceding conventional MRI changes or clinical strokes.[31,58]

### Electroencephalographic and EMG Studies

Many patients show electroencephalographic abnormalities such as the predominance of theta and delta frequency slowing, with a paucity of normal posterior dominant alpha frequency activity to suggest the presence of a diffuse white matter disease.[7] Electromyography studies can detect axonal neuropathy. Majority of these neuropathic changes are clinically silent and may have a spontaneous improvement in follow-up studies.[7]

## *Pathology*

### Dermatopathology

A skin biopsy can be particularly useful for the diagnosis of SS, especially in patients with only dermatological manifestation. Rather than a sampling of the discolored

peripheral ring, multiple deep large punch biopsies from the normal-appearing center of a prominent livido lesion can increase the detection rate of the arterial obstruction.[59] Myocytes migrate to the subendothelial region and proliferate to cause of the expansion of the subendothelial region and a near-total or total occlusion of medium- and small-sized arterioles of the dermis and hypodermis (subcutis).[60] Identification of these migrating cells is possible due to their strong positive staining for myocytic elements such as actin and vimentin. Thus in a true sense, subendothelial proliferation is a misnomer. However, rare observation of endothelial cell proliferation rather than myocytes was documented by Lewandowska et al.[61] Endothelial cell identification was done due to positive Weibel-Palade bodies and CD31 immunoreactivity – both markers of endothelial origin. Capillary lumen narrowing and angiogenesis were also noted in this histopathology sample. However, findings of angiogenesis and endothelial proliferation may be due to reactive changes from the hypoxia rather than from the true pathology of arteriolar obstruction due to myocyte proliferation. Due to arterioral obstruction, tissue hypoxia occurs with subsequent reactive venular dilatation.

Zelger et al described 4 sequential changes of the dermal histopathology and summarized in Table 3.[62] However, the presence of the first phase is not universally agreed upon as many authors did not notice significant inflammation in the histopathology samples. However, the caveat here is that a sampling of the tissue in the later stage of the disease can miss the earliest changes of the pathogenesis. Other rare reported dermatopathology is leukocytoclastic vasculitis and diffuse venular thrombosis.

### Neuropathology

Only a few neuropathological studies have been published. Though rare granulomatous inflammation has been reported, most papers confirmed findings of noninflammatory thrombotic vasculopathy involving medium- and small-size cerebral arteries comparable to the pathology noted in dermal arteries.[63,64] Multiple necrotic areas in the white and gray matter can be seen without inflammation or thrombosis if the biopsy is taken from an area of old infarction. Histopathology of other organ systems has been rarely described. Rare reports of cardiac valve histopathology showed dystrophic changes with the presence of microthrombus on the surface of the valve leaflets.[65-67] Macario et al described a kidney biopsy study with the presence of similar vascular pathology of dermal and cerebral arteries.[46]

## Differential Diagnosis

Diseases that can cause generalized LR or similar skin lesions are summarized in Table 4.

Several diseases can cause strokes in young adults and summarized in Table 1. However, strokes due to hypertension, cardioembolic strokes, due to migraine and use of oral contraceptives, and strokes due to isolated cerebral angiitis and systemic vasculitis are the closest differentials.

Combination of LR and recurrent strokes can also be seen in Divry van Bogaert Syndrome (DBS).[68] In contrast to DBS, true "angiomatosis" or neoplastic vascular proliferation is not seen in SS. Moreover, in contrast to SS, the familial occurrence is far more common in DBS.

## Treatment

Treatment of SS is primarily based on anecdotal reports. There have been no prospective controlled studies to guide therapy.[69] Estrogen-containing contraceptives have been associated with SS, but their effect on the onset or progression of the disease is unclear. Anecdotal reports suggest possible improvement of neurological symptoms after discontinuation of contraceptives. Several other factors such as pregnancy, smoking, diabetes mellitus, atherosclerosis, and hyperlipidemia have been suspected as potential risk factors, but conclusive evidence linking these risk factors to disease progression is lacking. However, controlling potentially modifiable risk factors is advisable.

### *Antiplatelet and Antithrombotic Agents*

Antiplatelet and antithrombotic agents are used for secondary stroke prophylaxis. SS with aPL positive patients are treated as primary aPL patients, and treatment with high-dose antithrombotic agent is recommended to reduce the risk of thrombosis.[70] High-dose warfarin with international normalized ratio (INR) > 3 is preferable in this situation. However, treatment of aPL negative SS is more controversial. Both antiplatelet agents (aspirin and

**Table 3.** *Zelger's proposed stepwise progression of skin histopathology in Sneddon syndrome*

| Stages | Histopathology |
|---|---|
| "Endothelitis" | Splitting of endothelium, perivascular inflammation, and marked edema of the surrounding connective tissue |
| Inflammatory obstruction | Occlusion of vascular lumen by mononuclear cells, RBCs, and fibrin |
| Subendothelial proliferation | Migration and proliferation of myocytes to the subendothelial region |
| Fibrosis | Organization of the cellular plug to a fibrotic plug with fibrosis of the occluded artery and shrinkage |

**Table 4.** *Differential diagnosis of patchy, net-like, violaceous skin discoloration*

| | Conditions associated with Livedo racemosa or livedo reticularis |
|---|---|
| Congenital | Physiological congenital cutis marmorata |
| Hematological state | Sneddon syndrome, antiphospholipid syndrome, cryoglobulinemia, polycythemia vera, essential thrombocythemia, disseminated intravascular coagulation (DIC), thrombotic thrombocytopenic purpura(TTP), other thrombophilic conditions (protein C, Protein S, and antithrombin III deficiency) |
| Autoimmune and connective tissue disorder | Polyarteritis nodosa, systemic vasculitis, livedo vasculitis, Wegner's granulomatosis, systemic lupus erythematous (SLE), Rheumatoid arthritis, dermatomyositis, systemic sclerosis, and Sjogren syndrome |
| Neoplasia | Lymphoma, leukemia, renal cell cancer, and breast cancer |
| Infection | Syphilis, meningococcemia, tuberculosis, brucella, hepatitis C, mycoplasma pneumonia, parvovirus B19, and coxiella burnetti |
| Other | Cholesterol emboli syndrome, pheochromocytoma, exposure to medicines such as amantadine, minocycline, and quinidine |

clopidogrel) and antithrombotic agents (warfarin) may have similar efficacy in the prevention of recurrent cerebral events in aPL negative patients.[6] But, antiplatelet agents have a better safety profile with a lower risk of hemorrhage compared to warfarin. Despite concern about intracranial hemorrhage, recombinant tissue-plasminogen activator has been used for acute thrombolysis safely in a small subset of patients.[71] Rare intracranial hemorrhage have been reported. However, it is currently unknown if the presence of collaterals or microbleeds increases the risk of hemorrhage and if the use of warfarin may be relatively contraindicated in this particular group.[72]

### *Other Agents for Treatment*

Presence of an inflammatory phase in the early stage of the disease has been hypothesized by some authors, but anti-inflammatory or immunosuppressive therapies such as corticosteroids and azathioprine are generally not beneficial and potentially harmful. However, Hannon et al reported one patient who had an improvement of the cognitive and emotional profile with the cyclophosphamide use.[55] Further studies are needed before the routine use of immunosuppressants in SS patients with cognitive decline. Angiotensin-converting enzyme inhibitors are recommended for systemic hypertension.[73] It may prevent myocyte migration and proliferation in the subendothelial region. Several agents have been used to reduce the viscosity of the blood with improved blood flow to treat dermatopathology. Anecdotally, immunoglobulin, rivaroxaban, nifedipine, and prostaglandin E1 (alprostadil) have been used for cutaneous manifestation including skin ulcers.[74] A low dose of antipsychotics can be effective in SS-related psychosis.[30] Successful surgeries for different indications including heart valve replacement have been reported with proper anesthetic care.[75] Nagai et al reported that macular edema and optic disc macroaneurysm associated with SS could be successfully treated with a subtenon injection of steroid (triamcinolone), suggesting an inflammatory process in the pathogenesis.[76]

## Prognosis

Neuropsychiatric prognosis of SS is relatively poor. Though motor deficit generally improves with time and does not cause severe handicap, after a variable period, dementia and cognitive impairment set in to produce moderate to severe disability. Cognitive deficit correlates with MRI features of cortical atrophy, which may have a parietal-occipital region predominance.[24] A broad range of neuropsychiatric deficits is detected with predominant involvement of concentration, attention, visual perception, and visuospatial skills.[77] In some cases, a pure deficit in concentration or attention may mimic primary memory dysfunction. Earlier and more severe involvement of performance intelligence quotient (IQ) is reported compared to the verbal IQ. Majority of patients lose employment due to cognitive deficits rather than motor difficulties. The rate of cognitive worsening varies from patient to patient but perhaps depends on the number of recurrent strokes and the rate of cerebral atrophy. In general, the cognitive prognosis of SS is poor compared to other nonprogressive conditions (cardioembolic strokes, strokes associated with hematological diseases) associated with strokes in young adults. However, a recent study showed relatively better prognosis with a comparable stroke recurrence risk over 6.5 years to an age-matched sample.[6] The relatively better prognosis perhaps resulted from the universal use of antiplatelet/antithrombotic agents for secondary stroke prophylaxis.

## Sneddon Syndrome in Children

The presentation in pediatric patients is similar to adults, and dermatologic manifestations are usually apparent for many years before the onset of recurrent strokes. Though most patients with SS are diagnosed after 20 years of age, a substantial number of them may have

LR in the pediatric age group, particularly during or after puberty. However, a relative unawareness of this condition among pediatricians and pediatric subspecialists lead to significantly delayed diagnosis. Most of the data in pediatric SS came from the limited number of case reports. Several reports describing SS in boys are present, and the typical female predominance seen in adults may not exist in children, especially when the onset is in the first few years of life. There is also the additional risk of intellectual impairment in children with SS, especially with early-onset recurrent strokes. Negative laboratory workup including negative aPL might be more prevalent in children, as well as the risk of seizures; however, without a large cohort, a definitive conclusion cannot be reached.

Children who presented in the first decade of life may have congenital LR lesion, which can be misdiagnosed as cutis marmorata. Diagnosis of SS is usually possible after the onset of recurrent strokes. Mathias et al reported 2 unrelated children (1 boy and 1 girl) who presented between 2 and 3 years of age due to recurrent strokes but had prominent LR since birth.[78] Both of them also had a moyamoya pattern on the angiography. They had unremarkable laboratory workup. Gruppo et al reported another SS patient with the onset of seizures and strokes from the age of 7 months.[79] She also had congenital LR and moyamoya syndrome. In contrast to the 2 patients described by Mathias et al, this patient was tested positive for factor V Leiden mutation. Wheeler et al reported a 7-year-old with congenital LR and strokes, with negative anticardiolipin antibodies.[80] Additional findings reported in this patient were obesity, intellectual impairment, hypertension, polycythemia, and enlarged cystic kidneys. His MRA and other workup were normal. Buxter et al reported 3 patients of age 8, 17, and 21 years with SS; all of them had pronounced congenital LR lesion.[81] Parmeggiani et al reported a biopsy-proven SS patient.[82] This male child was born to consanguineous parents after a complicated pregnancy due to chronic placental insufficiency. Congenital LR lesion was present. He had his first stroke at the age of 7 when MRI of the brain also showed diffuse white matter hyperintensity, including involvement of the pons and basal ganglia. His laboratory workup was negative including negative aPL antibodies except for a diagnosis of arylsulfatase A pseudo deficiency. The significance of his atypical neuroimaging abnormality was unclear.

Symptom onset in the pubertal children also has been described, especially when the interval between dermatological manifestation and recurrent strokes is short. Gottlober et al reported a 16-year-old girl with left-sided hemiparesis from SS.[83] She developed LR 5 months before her stroke. She had a negative workup including negative aPL antibodies and anti-nuclear antibody. Zaccarioti et al described 2 unrelated boys aged 7 and 16 years with SS.[84] The 7-year-old presented with seizures and stroke, and the 16-year-old had hemifacial seizures as well as strokes involving the brain stem. They also tested negative for aPL antibodies.

Familial occurrence with one parent and a child or siblings with clinical features consistent with SS has been reported. Lousa et al reported a child and her father with SS, both of them experienced a significant reduction of stroke recurrence with an oral anticoagulant, which was started after aspirin failed to prevent recurrent episodes of TIAs.[85] Pettee et al similarly described 2 brothers with good response from an anticoagulant agent.[86]

## Conclusions

SS is a rare disease of unknown etiology with striking dermatological manifestation and recurrent strokes. Recent research suggests that the prognosis of stroke recurrence might be better compared to the historical data due to the increasing use of antiplatelet/antithrombotic agents for secondary stroke prophylaxis. However, long-term data are needed to see an improvement in the cognitive profile with decreasing stroke recurrence. As several manifestations can precede strokes by several years in SS, an awareness of those features and the adoption of a primary prevention approach such as aggressive control of hypertension and avoiding hormonal contraceptives may be helpful. Further research to explore genetic susceptibility including ADA2 deficiency, the cause of predominance in young women and the role of novel biological therapy such as anticytokine therapy is needed.

## Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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