

# Therapy of Sneddon Syndrome

Agnes Flöel Tanya Imai Hubertus Lohmann Florian Bethke  
Cord Sunderkötter Dirk W. Droste

Department of Neurology, University of Münster, Münster, Germany

## Key Words

Sneddon syndrome · Epilepsy · Cognition ·  
Anticoagulation · Antiplatelet therapy

## Abstract

We report the case of a young woman with progressive cognitive decline and epilepsy. She showed ischemic cerebrovascular disease and proximal livedo racemosa. Antiphospholipid antibody (aPL) could not be detected and there were no microemboli on continuous transcranial Doppler ultrasonography monitoring. Histology of cerebral vessels showed intimal hyperplasia in small leptomeningeal venous vessels and micronecrosis of grey and white matter. We subsequently made the diagnosis of aPL-negative Sneddon Syndrome (SNS). Anticoagulation with warfarin could not be initiated because of a drug-resistant epilepsy with the risk of falls and subsequent bleeding; immunosuppression with steroids and azathioprine was ineffective, as was initial antiplatelet therapy with clopidogrel alone. However, when we intensified antiplatelet therapy by combining clopidogrel and ASS, a slowing of disease progression, as assessed by neuropsychological testing and magnetic resonance imaging, was noted on a follow-up after 6 months. Therapeutic options in SNS in both aPL-positive and aPL-negative patients with SNS are discussed.

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## Introduction

Sneddon syndrome (SNS) is characterized by the association of ischemic cerebrovascular events with widespread livedo racemosa primarily on the trunk [1]. The presence of several other organ manifestations such as cardiac and kidney lesions suggests that it is a systemic syndrome [2].

Livedo racemosa is a cutaneous sign consisting of striking violaceous, netlike-patterned erythemas of the skin, with irregular, broken circular segments. It is localized on both trunk and extremities and persists on warming [3]. It results from persistent and irregular focal impairment of the blood flow in cutaneous vessels, e.g. due to partial or complete occlusion or to increased viscosity, and can be found in atherosclerosis, vasculitis, or SNS.

The onset of cerebrovascular events in Sneddon syndrome usually occurs before the age of 45 years. Hemiparesis, hemisensory symptoms, dysphasia, and visual symptoms are common. As medium-sized arteries are mainly affected, strokes are rarely fatal, and good recovery is observed initially. However, recurrent events frequently lead to functional disability and vascular dementia. Approximately half of the patients report of headache. Cranial magnetic resonance imaging (MRI) detects cortical, subcortical or cortico-subcortical abnormalities suggestive of arterial ischemic infarcts which are frequently multiple [2, 4]. Usually, periventricular white matter changes

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Agnes Flöel, MD  
Department of Neurology, University of Münster  
Albert-Schweitzer-Strasse 33  
D-48129 Münster (Germany)  
Tel. +49 251 834 9969, Fax +49 251 834 8181, E-Mail [floel@uni-muenster.de](mailto:floel@uni-muenster.de)

are observed [5]. Diffuse cortico-subcortical atrophy is observed in late stages of the disease. Heart valve abnormalities are detected in half of the patients [4]. Both aortic and mitral valve lesions may occur [4]. Mild to moderate systemic hypertension has been found in approximately 60% of patients with SNS. Venous thrombosis occurs in 15% of patients [4]. Decreased creatinine clearance and even chronic renal failure has been reported [6].

The prevalence of antiphospholipid antibodies (aPL) in SNS has been reported to range from 0 to 85% depending upon the series [4, 6]. Patients with SNS and aPL are more likely to develop epilepsy (30% in aPL-positive vs. 10% in aPL-negative cases [2]). Optimal management of patients with SNS remains an unsolved problem. Prospective randomized controlled trials are not available [7]. Therapeutic management is based either on treating detectable anomalies of the coagulation system such as aPLs (inference from treatment of single patients with aPLs), or is based on pathophysiological assumptions. Positive effects of anticoagulation, antiplatelet therapy and immunosuppression, alone or in combination, have been observed, but they were often minimal at best. Slowing down or even reversing the cognitive decline has rarely been possible [7]. Concomitant diseases which carry an increased risk of bleeding, such as epilepsy with an increased risk of falls, uncontrolled hypertension, poor compliance, liver disease, peptic ulcer and previous cerebral hemorrhage have to be considered in each patient with SNS [8, 9].

In the present study, we report on a young woman with aPL-negative SNS and drug-resistant epilepsy. Her clinical course under different treatment regimens is described, followed by a general discussion of treatment options in SNS.

## Case Report

A 29-year-old woman (D.N.) presented to the department of neurology with a 5-year history of focal epilepsy with secondary generalization, which had proven pharmacoresistent despite various antiepileptic drug regimes, including carbamazepine, valproic acid, lamotrigine, phenytoin, gabapentin and topiramate. Additionally, there was a progressive 3-year decline in cognitive function. She had poor concentration, easy fatigue and increasing difficulty in word retrieval. This had led to her quitting a secretary trainee program in August 1998, and she had had no employment since then. Lately, she had had difficulties coping with everyday household work and her 8-month-old baby.

Her medical history was significant for elevated arterial blood pressure since the age of 18, a chronic tension headache and atopic dermatitis. No stroke-like episodes were reported. There was no

family history of skin lesions, cognitive dysfunction and stroke-like events.

On physical examination, the patient (84 kg, 174 cm) was in a reduced general state of health. Her blood pressure was 140/96 mm Hg. The neuropsychological assessment revealed a significant decline since her first neuropsychological evaluation 2 years ago (table 1, 1st examination). Her main problems had then been reduced mental speed, reduced mental flexibility and impaired word production ('verbal fluency'). Other functions, including long-term memory, immediate and delayed recall, language, visuospatial abilities, praxis and judgement had either been average or above average. Now, she showed a predominantly dysexecutive syndrome [9], i.e. mental flexibility was moderately impaired. Verbal and spatial working memory and selective attention were severely impaired. Mild behavioral changes were also noted. Other higher cognitive functions (language, visuospatial abilities, praxis, judgement) were unimpaired (table 1, 2nd examination).

Her motor examination showed weakness and dysdiadochokinesia of the left arm. Her tendon reflexes were brisk but symmetrical, coordination and sensation were normal. She had livedo racemosa on the back of the upper arms and on the back of the legs (fig. 1). These skin signs were discrete and had not been noted before. Skin biopsy revealed small vessels in the subcutis with a reorganizing small thrombus, and other small vessels showed an endothelial thickening. There were no signs of an inflammatory process, especially no signs of vasculitis (fig. 2). MRI of the brain showed bihemispheric confluent signal increases on T<sub>2</sub>-weighted and proton-density images in cortical regions and parieto-occipital subcortical white matter (fig. 3).

On MR spectroscopy, she had neuronal degeneration (N-acetyl-L-aspartate reduction), but no lactate increase. Therefore, a mitochondrial encephalopathy with lactic acidosis and stroke-like episodes was highly unlikely. EMG was normal. Muscle biopsy showed an unspecific mild type-II atrophy. Doppler ultrasonography of the intra- and extracranial arteries was normal. There were no clinically silent circulating microemboli on 1-hour continuous transcranial Doppler monitoring of both middle cerebral arteries. Transthoracic echocardiography showed a tricuspid aortic valve with insufficiency grade 1, and a minimal tricuspid valve insufficiency. An MRI-guided stereotactic brain biopsy yielded only inconspicuous brain tissue. However, a subsequent CT scan of the head revealed that the biopsy had been taken slightly off the lesion. Therefore, a second MRI-guided stereotactic brain biopsy was performed, which showed multiple, predominantly older and mostly incomplete micronecroses of grey and white matter and a white matter degeneration. These changes were due to intimal hyperplasia in small leptomeningeal veins, most likely secondary to disseminated thromboses with recanalization (fig. 4). Extensive laboratory studies uncovered no evidence of vasculitis, hypercoagulable state, or toxic metabolic disturbances. The following tests were all normal: full blood count, coagulation tests including detection of antithrombin III, protein C, and protein S deficiency, homocysteine blood levels ( $N \leq 12 \mu\text{mol/l}$ ), fasting serum glucose, complement (CH50, C3, C4), cryoglobulins, cryofibrinogen, rheumatoid factor, antineutrophil cytoplasmic antibodies and serum immunoelectrophoresis. Lupus anticoagulant and anticardiolipin antibodies (IgM and IgG) 1 and 2, and beta 2 glycoprotein I were found normal on five occasions in a 1.5-year period.

The patient was diagnosed as having aPL-negative SNS. Anticoagulation, antiplatelet and/or immunosuppressive therapy were considered. Since no coagulopathy had been detected and the patient

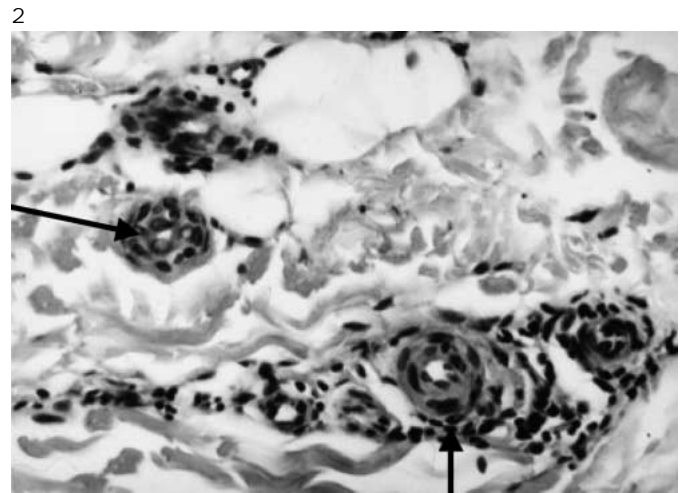


Fig. 1. Photograph of the right upper arm of patient D.N. Her livedo racemosa presents as a violaceous, broken rash.

Fig. 2. Skin biopsy of patient D.N. (hematoxylin-eosin, original magnification:  $\times 32$ ). Histology reveals small vessels in the subcutis with endothelial thickening (arrow).

Table 1. Neuropsychological evaluations of patient D.N. over the course of 38 months

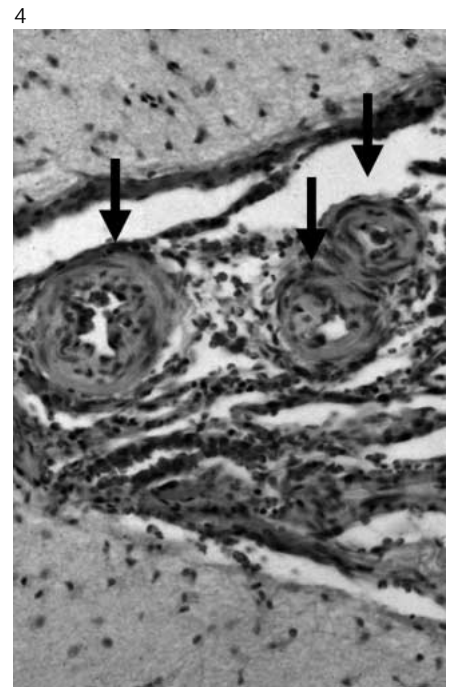
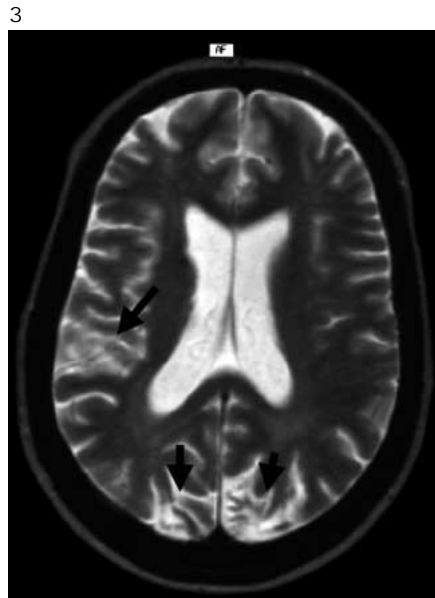
Examination number	Current medication (antiepileptic/ immunosuppressive and antiplatelet)	Working memory, percentile <sup>1</sup>			Verbal learning and memory, percentile			Attention, percentile			Executive functions, percentile		
		digit span (WMS-R)	digit span revised order (WMS-R)	word span (RAVLT)	new learning	retrieval short-term	retrieval long-term	mental speed (TMT, part A)	sustained attention, speed 'd2'	sustained attention, accuracy	flexibility (TMT, part B)	lexical fluency (COWA)	set shifting, flexibility ('P-ZOO-Task')
1st	phenytoin, carbamazepine/none	30	30	90	80	95	90	<10	58	>90	<20	20	30
2nd 24 months later <sup>2</sup>	phenytoin, carbamazepine/none	10	25	75	10	5	10	<10	18	>90	0	<5	10
3rd 26 months later <sup>2</sup>	valproic acid/start of steroids, azathioprine, and aspirin	30	30	85	60	50	35	<10	42	>90	<20	<5	15
4th 32 months later <sup>2</sup>	valproic acid/steroids, azathioprine, and aspirin	5	5	50	20	25	10	<10	18	>90	<10	<5	10
5th 38 months later <sup>2</sup>	valproic acid/ aspirin and clopidogrel	5	5	75	20	20	5	20	50	75	<20	<5	10

WMS-R = Wechsler Memory Scale – Revised; RAVLT = Auditory Verbal Learning Test; WAIS-R = Wechsler Adult Intelligence Scale – Revised; TMT = Trail Making Task; COWA = Controlled Oral Word Association.

<sup>1</sup> Percentile: e.g., the 75th percentile is a score that is equal to or better than 75% of all subjects who were tested.

<sup>2</sup> Time span after first examination.

Fig. 3. Axial, T<sub>2</sub>-weighted cranial MRI of patient D.N. In the frontal and parieto-occipital cortical regions and subcortical white matter, bihemispheric confluent signal increases on T<sub>2</sub>-weighted images can be seen. Fig. 4. Small leptomeningeal blood vessels showing marked endothelial hyperplasia (arrow) (hematoxylin-eosin, original magnification: ×64).



had a high risk of falls with subsequent intracranial hemorrhage because of her drug-resistant epilepsy, we decided against warfarin anticoagulation. An antiplatelet agent (clopidogrel, 75 mg per day) was given. More aggressive therapies like immunosuppression were discussed with the patient and her family. Primarily because of the rapid cognitive decline over the last 2 years, a therapeutic immunosuppressive trial (steroids plus azathioprine) was started ex juvantibus.

Additionally, her antiepileptic medication was changed; most importantly, medication that caused drowsiness (carbamazepine, phenytoine) was reduced. Subsequently, under valproic acid medication only, she improved significantly on working memory and learning tasks, but still showed a dysexecutive syndrome (table 1, 3rd examination).

She returned to hospital 6 months later because of dizziness, nausea and diplopia that began after an increase in her antiepileptic medication (valproic acid) 10 days before admission, and which disappeared after reduction of valproic acid.

She also reported a further decline in memory and concentration over the past 6 months. On neurological examination, she showed slurred speech and weakness of the left arm, which persisted after reduction of her antiepileptic medication. On neuropsychological assessment, she had a dysexecutive syndrome with decline in mental flexibility, working memory and selective attention (table 1, 4th examination). An MRI of the head revealed a progression of frontal, occipital, temporo-occipital and cerebellar lesions. Additionally, a fresh lesion with blood degradation products in the right striatum was noted, consistent with an infarction in the previous 2–3 months. In summary, no slowing in disease progression was observed since the initiation of antiplatelet and immunosuppressive therapy 6 months ago. Therefore, the potentially dangerous immunosuppressive therapy with azathioprine (increased risk of infection, induction

of carcinomas) was stopped. Antiplatelet therapy was intensified by adding aspirin (50 mg per day) to clopidogrel.

Six months later, the patient was seen in our outpatient clinic. She did not complain of any further cognitive decline. Neuropsychological examination did not reveal any significant changes compared with the testing 6 months ago (small improvement in attentional tasks, deterioration in verbal learning and memory tasks) (table 1, 5th examination).

## Discussion

SNS is clinically defined as the combination of livedo racemosa and cerebrovascular events [1, 11]. Because no specific test for SNS exists, clinical differentiation from other phenomenologically similar disorders may be difficult and has raised controversy [2, 11–15]. Various neurological problems have been associated with SNS and aPLs, including cerebrovascular events, chorea, seizures, myelopathy, atypical migraine-like events, acute encephalopathy, and dementia [3, 4, 12, 16, 17].

The first manifestation of disease in our patient was drug-resistant epilepsy, followed by progressive cognitive decline. Skin lesions were discrete, no coagulopathy was detected. The patient did not present with acute cerebrovascular events. However, her cranial MRI suggested that a number of microinfarctions had taken place in the preceding years. Neither the signal pattern nor the distribu-

tion of white matter lesions were specific for SNS. Similar findings may be seen in other cerebrovascular disorders affecting small arteries [3]. The diagnosis of SNS was ultimately confirmed on brain (and skin) biopsy.

Stereotactic brain biopsy is invasive and carries a small but definite risk of morbidity and even mortality. Nevertheless, we opted for a brain biopsy, first to exclude any treatable disease, and second to confirm the diagnosis of SNS. The options for treatment of SNS, anticoagulation, antiplatelet and/or immunosuppressive medication are all long-term treatments, and carry a substantial risk themselves. Therefore, in patients without aPLs, the decision about potentially harmful therapies should be based on a definite diagnosis. Skin biopsy, which is much less invasive, has been reported to yield no abnormalities on histological examination in the majority of patients in a study of 44 patients [4]. Not all studies agree on the validity of brain biopsy in diagnosing SNS. A recent study by Zipper et al. [18] reported inconclusive results for brain biopsy. However, brain biopsy might not have been carried out by an experienced examiner, and therefore the biopsy might have missed the relevant area. Even a slight deviation from the lesion area might lead to inconspicuous results (see Case Report).

The pathogenic mechanisms in SNS and primary antiphospholipid syndrome are incompletely understood [12, 19]. A defective vascular endothelium, alone or in combination with a slight or nondetectable coagulation deficit, might traumatize the endothelium [4, 12, 20, 21]. The presence of aPLs, most notably anticardiolipin antibodies and lupus anticoagulant, may be detected in about half of the SNS patients, with a range from 0 to 85% depending on the series [4, 6]. Their presence suggests that SNS results from a thrombotic process [4, 12]. A number of authors have found noninflammatory endothelial proliferation and fibro-mucinous changes with subsequent occlusion of small vessels [20]. Monitoring the middle cerebral artery using transcranial Doppler ultrasonography (TCD) showed clinically silent microembolisms in 38% of patients with SNS, all aPL-positive [22].

In aPL-negative cases, a primary inflammatory process has been suggested [3, 4, 21], though a number of studies did not show inflammatory changes on skin and brain biopsies [11, 14], and the inefficacy of immunosuppressive therapies argues against a primary inflammatory vascular process in SNS.

Varying findings on microscopy might be due to different underlying disease processes in patients clinically diagnosed with SNS [2]. It might also be due to sampling in different stages of the disease [23].

A recent review [2] suggests that aPL-positive and aPL-negative SNS patients show distinct clinical and biological features. In aPL-positive patients, seizures and clinically audible mitral regurgitation are more frequently observed, the fishnet of the livedo is larger, and thrombocytopenia is present in about one third of patients [4]. In comparison, thrombocytopenia has never been reported in aPL-negative patients [2, 4, 14].

Treatment of patients with SNS is still controversial. Categorization of SNS patients into two subsets (aPL-positive and aPL-negative), as described above, might influence disease management.

aPL-positive SNS patients might be treated like primary antiphospholipid syndrome. In primary antiphospholipid syndrome, patients with the highest titers of aPLs seem to have the greatest risk of recurrent thrombotic events [12, 19]. A wide variety of treatments including antiplatelet agents, anticoagulants, corticosteroids, immunosuppressants has been tried, but no prospective randomized controlled trials are available to guide management. A retrospective analysis of patients with primary antiphospholipid syndrome suggested that long-term anticoagulation is advisable, with the INR maintained at 3 or higher [2, 22, 24]. Therefore, in aPL-positive SNS patients, high-dose warfarin (INR  $\geq$  3) is currently mostly used [2, 4, 25–27].

Optimal management of aPL-negative SNS remains an unsolved problem [2]. In a study on aPL-negative patients with SNS, the number of cerebral events was lower with antiplatelet therapy; antiplatelet therapy was as effective as high-dose warfarin [4]. Frances et al. [4] suggested that antiplatelet therapy might slow cognitive decline in aPL-negative SNS patients, based on the observation that the only patient in their study who developed frank dementia (of the vascular type) was the one who did not receive antiplatelet therapy.

Wohlrab et al. [28] suggested the use of a triple therapy, i.e. in addition to antiplatelet therapy, angiotensin-converting enzyme inhibitors (ACE inhibitors) and prostaglandin E<sub>1</sub> are to be given. ACE inhibitors are posited to reduce angiotensin II-mediated proliferation and migration of subendothelial vascular myocytes. Prostaglandin E<sub>1</sub> might improve microcirculation by altering the rheological properties of the blood. The authors reported 5 patients treated with the triple combination who did not show further clinical deterioration over the course of 3–5 years.

In both aPL-positive and aPL-negative cases, limited effectiveness [3, 11, 14, 25] or frank inefficacy [13] of various immunotherapies, including steroids and azathio-

prine, has been repeatedly described. The use of corticosteroids and immunosuppressives without antithrombotic agents seems to be deleterious as noted in 6 previously reported patients [4, 26]. A temporary improvement with high-dose corticosteroids and aspirin has been reported [18].

The symptom most difficult to treat in both aPL-positive and aPL-negative patients is cognitive decline [5, 29]. Mental deterioration is not only one of the most common symptoms in SNS, but also one of the most important as far as quality of life is concerned. It ranges from moderate cognitive impairment [3, 5, 16] to frank dementia [3, 5]. Dementia in SNS occurs on a multi-infarct basis [16, 28]. Rare cases of more gradual cognitive decline without specific acute cerebrovascular episodes have also been reported [29, 30]. On imaging, these cases show widespread changes in the form of cerebral infarction.

Apart from aPLs, clinically silent microembolism has been posited to provide subclinical evidence of active disease in SNS patients, and might therefore guide therapeutic approaches [22]. However, in our patient, no microemboli were detected; still, the disease was clearly progressive, both clinically (further deterioration in mental flexibility, working memory and selective attention) and on cranial MRI (progression of size of white matter lesions, fresh lesion in the right striatum). This finding argues against a mechanism of arterio-arterial or cardiogenic microembolism as the pathomechanism in our patient. Intravascular, in situ thrombosis seems more likely here [22]. Taken together, the absence of microembolic

signals on continuous TCD monitoring does not argue against antiplatelet therapy.

In summary, patients diagnosed with SNS are to be screened for antiphospholipid antibodies, arterial hypertension (24-hour blood-pressure monitoring and ophthalmoscopy), renal dysfunction (creatinine clearance) and heart valve abnormalities (echocardiography).

Therapeutically, aPL-positive patients should be started on high-dose warfarin (INR  $\geq 3$ ). If warfarin is contraindicated because of a concomitant disease, antiplatelet therapy, ideally in the combination of two different agents (ASS and clopidogrel), is the most appropriate alternative.

In aPL-negative patients, antiplatelet therapy, again in combination, should be administered.

In both aPL-positive and aPL-negative patients, if disease is rapidly progressive despite therapy, ACE inhibitors and prostaglandin E<sub>1</sub> might be given. Ultimately, immunosuppressive agents like steroids and azathioprine can be tried, but always in combination with antithrombotic treatment.

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