

Original Article

Sneddon's Syndrome: Clinical and Laboratory Analysis of 10 Cases

Ertugrul Bolayir^{a*}, Abdulkemir Yılmaz^b, Nesim Kugu^c, Haydar Erdogan^d,
Melih Akyol^e, and Aytekin Akyuz^a

^aDepartment of Neurology, ^bDepartment of Emergency Medicine, ^cDepartment of Psychiatry, ^dDepartment of Ophthalmology, and ^eDepartment of Dermatology, Cumhuriyet University Faculty of Medicine, Sivas, Turkey

Sneddon's syndrome is characterized by livedo reticularis and cerebrovascular lesions. We report the cases of women (mean age, 36.2 ± 8.1 years) diagnosed with Sneddon's syndrome based on the presence of livedo reticularis and characteristic cerebrovascular findings. Seven of these patients had cerebral infarcts on cranial computed tomography scan. Antiphospholipid antibodies were positive in 6 of these cases. Three cases had abnormal levels of antithrombin III. Analyses of chromosome 6 revealed no abnormalities. In 3 of the cases, investigation of the pedigrees revealed autosomal dominant traits. Two cases had epilepsy, and 3 had migraine. One case with migraine also had myasthenia gravis. In addition, we detected inferior altudinal hemianopia in 2 cases, cognitive functional disorder in 3 and depression in 2. Based on these findings, the entire vascular, haematologic, neurologic, and dermatologic systems should be evaluated in patients diagnosed with Sneddon's syndrome.

Key words: Sneddon's syndrome, antiphospholipid antibodies, genetics, cognitive functions, migraine

Sneddon's Syndrome (SS), an uncommon disorder, is characterized by multiple cerebrovascular accidents, idiopathic livedo reticularis, and ischemic stroke, particularly in the territory of the middle cerebral artery. Seizures occasionally occur in the last term of the disease. Cognitive impairment is likely related to recurrent stroke leading to vascular dementia. The reason why SS tends to occur in dermal and intracranial cerebral vessels remains uncertain [1, 2].

SS is common in women between 20 and 42 years old. In addition to cerebral and dermatologic lesions, it may be accompanied by memory disturbances, hypertension, and retinal vascular obstructions [3-6]. It has been observed

that the pathogenesis of SS is able to have antiphospholipid antibodies, anticardiolipin antibodies and lupus anticoagulant [1, 2, 7]. Single or multiple infarcts can be seen on cranial CT or MRI imaging [5, 8, 9]. The characteristic skin lesions of SS are called livedo reticularis and the color difference may be seen in patched extremities, face, and trunk. The disease causes many neurologic and systemic disorders [2, 4-6].

In addition to livedo reticularis, several other lesion types, peripheral and cenral embolic lesions, retinal embolism, and other skin lesions are also included among the diagnostic criteria of this syndrome. In order to make an accurate diagnosis, all of the following must be performed: imaging cranial CT/MRI, carotid Doppler ultrasonography, cerebral angiography, laboratory studies, antiphospholipid antibodies, VDRL, serum protein electrophoresis, antithrombin III and cryoglobulin

assay, and skin biopsies [1, 5, 8, 10, 11].

In this study, we report on the clinical, radiologic, genetic and laboratory analysis of 10 cases of SS, and provide a review of the relevant literature.

Materials and Methods

Patients with SS admitted to the Neurology Department of our institution were questioned about their family and personal disease-history. Systemic, neurologic, dermatologic, visual and psychiatric examination of the patients was performed. Routine blood and urine analysis, muscle and liver enzymes, lipid profiles, protein electrophoresis, serologic and rheumatologic tests, coagulation profiles, C3 values, cryoglobulins, LE cells, anticardiolipin antibodies, lupus anticoagulants, protein C and Ss, antithrombin IIIs, VDRLs, thyroid hormones, routine skull and lung X rays, cranial CTs, cerebral and ocular ultrasonographies (EUB 515A Doppler USG), standard EEGs, ECGs, and cardiologic examinations were all studied. Skin biopsies from lesions were obtained from all patients. The following stains were used in the skin biopsies: Haematoxylin and Eosin (H and E), Masson trichrome, PAS, and Orcein stain for elastic tissue. The evaluation of the neurocognitive functions of these cases, minimal state test, Bender-Gestalt visual motor perception test, and Wechsler adult intelligence scale-Turkish version were performed, and SCID-1 was also performed to determine DSM-IV I axis psychiatric diagnosis. Ophthalmological examinations were performed in all cases. Visual acuity and biomicroscopic examination were performed. Intraocular pressure was measured by Applanation tonometer. Color vision examinations were made using a 100 Hue test. Visual field was assessed by automated static threshold perimetry using Humphrey analyses program 30-2. All patients were administered cyclopentolate 1% eye drops in each eye before funduscopic examination. Slit lamp biomicroscopy using a 78D lens was performed by an ophthalmologist.

Chromosome analysis was performed on cultured lymphocytes from peripheral blood with conventional GTG and CBG banding techniques, and pedigree analysis of all patients was also performed.

Results

All cases were women, and all of them had a history of stroke. Their average age was 36.2 ± 8.1 years. All

cases had livedo reticularis, and three patients had a history of smoking one packet of cigarettes per day one of these patients had been smoking a packet of cigarettes a day for 5 years, and the other 2 had been doing so for 2 years. We detected hemiparesia and hemihypoesthesia in 7 cases, dysphasia in 2 cases, and amourosis fugax in 1 case. The 4th and 10th cases had hemiparesis, and hemihypoesthesia was recovered within 24 h in both these cases. We detected epileptic seizures in 2 cases; one of these (case 2) had a generalized tonic-clonic seizure, and the other (case 3) had a focal type seizure. Three cases having a history of headache were evaluated according to IHS criteria and diagnosed as cases of migraine with aura. Two patients had primary infertility, one patient was unmarried (this patient could not have had children because she was unmarried), and the other cases had a history of at least 2 abortions in the first or second trimester. Antiphospholipid antibodies were positive in 6 cases.

One patient had Myasthenia gravis (MG); cranial computed tomography (CT) scan analysis of this patient revealed thymic hyperplasia, and effort test and neostigmine test results were positive. In addition, this patient also showed positivity for acetylcholine receptor antibodies. In the neostigmine test (with 1.5 mg neostigmine and 0.6 mg atropine sulphate I.M.), partial ptosis was clearly improved beginning at 20 min after the start of the test, with the improvement peaking at 45 min after the start of the test. A typical decrement response (more than 20%) was obtained by 3.5 and 10 Hz repetitive stimulation of nasal muscle. Single fiber EMG showed jitter values of 116, 207, and 140 μ s in 3 motor unit potentials with a block rate of 50–60%, which values have a also recommended for the diagnosis of MG. Four of the patients were diagnosed with hypertension, and 2 of these had mitral stenosis.

Antithrombin III values were above the normal range in 2 cases and below the normal in one case. The biopsy samples obtained from the lesional skin revealed thrombosed capillary veins in 4 cases. The skin biopsies had a normal appearance in the other cases.

Cranial CT scan revealed hypodense areas localized to the left middle cerebral artery region in 4 cases and multiple infarcts in 3 cases.

Ultrasonographic examination of carotid and ocular arteries revealed a low flow pattern of the left ophthalmic artery in 2 cases. In 1 case, the bilaterally intact common carotid artery (CCA), intra carotid artery (ICA), and

extra carotid artery (ECA) lumens, but the flow pattern of the right ophthalmic artery was found to decreased, while that of the left ophthalmic artery increased.

Epileptic discharges were detected in the EEGs of 2 cases. Two cases showed altitudinal hemianopia on visual field examination. Two cases showed visual motor perception disturbance on Bender-Gestalt test and mild mental retardation. Three patients had depression according to SCID-1 criteria.

The results of fundoscopic examination, intraocular pressure, and color visual field examinations were all normal. Visual acuity was 20/20 in all patients.

Chromosome 6 analysis was normal in all cases. With regard to the obtained pedigrees, the parents of case 6 were cousins and the mother had SS (Fig. 1a). Case 10 was the daughter of case 9, and the family history revealed that the grandmother of case 10 (i.e., the mother of case 9), had SS (Fig. 1b). Results for a representative case, case 1, are presented in Fig. 2; the livedo reticularis lesions present on lower extremities, as well as the results of skin biopsies and CT scans are shown. The findings of all cases are summarized in Table 1.

Discussion

SS is a rare syndrome characterized by idiopathic livedo reticularis and cerebrovascular disease [12]. It is generally seen in women between the ages of 20 and 42

years, although it is sometimes seen in girls as young as 10 or women as advanced as 64 years. It is rare in men. The incidence of cases is 4 per 1 million [4]. The primary focal thrombotic or embolic processes and autoimmunity play a role in the pathogenesis of SS [3, 4, 6, 7, 13-17]. In the serial studies reported by Sneddon [1], all 6 patients were women, and in the report by Rebello [5], 7 of 8 patients were women. In our study, all patients were women.

Since arterial and venous complications of unknown etiology are seen in SS, symptoms of ischemic encephalopathy, visual disturbances, and headache are also sometimes present [13, 18]. Headache is often seen in SS cases, and this event increases the risk of stroke [19, 20].

Rebollo *et al.* reported broad and medium-sized arterial damage in 8 cases of SS characterized by angiographically determined livedo reticularis and cerebrovascular disease, and normal skin biopsies; 7 of these cases also showed a focal hypodense area in conformity with infarct by CT imaging [5]. Two studies have reported cases with multiple infarct, sporadic transient ischemic attack, or recurrent ischemic attack [21, 22]. One study reported that headache-most frequently migraine-was present in 50% of 133 cases [19]. Thomas *et al.* reported 1 case of SS with associated hypertension [5], and Stephan *et al.* [21] and Rebollo *et al.* [23] reported 2 and 6 such cases, respectively. In our study, livedo

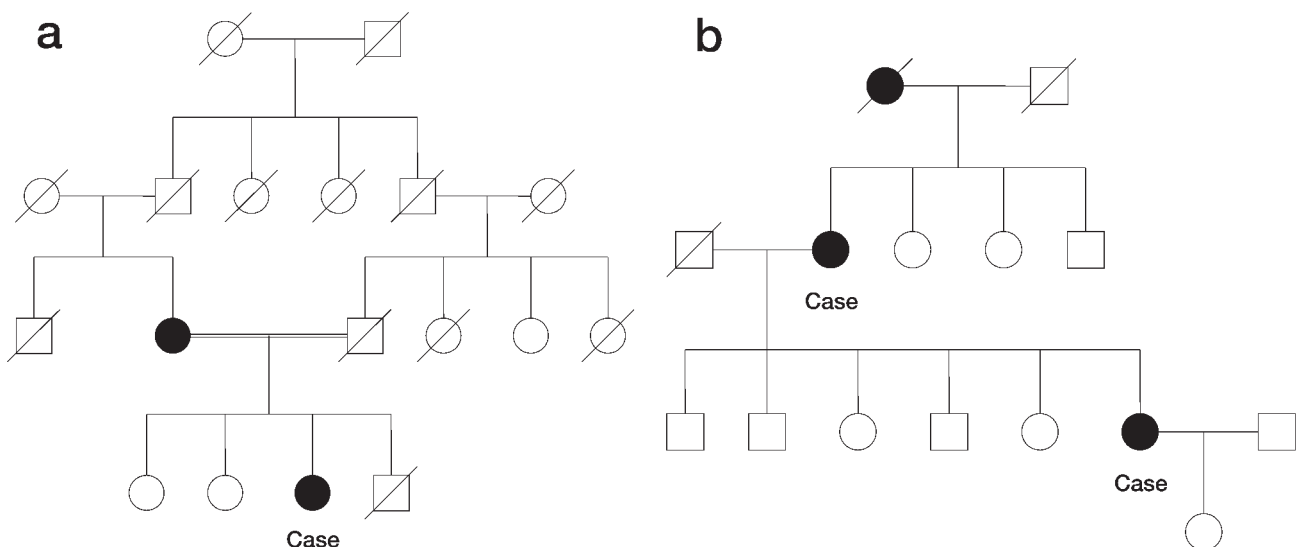


Fig. 1 The parents of case 6 were cousins and the mother had SS (a). Case 10 was the daughter of case 9, and the family history revealed that the grandmother of case 10 (i.e., the mother of case 9) also had SS (b).

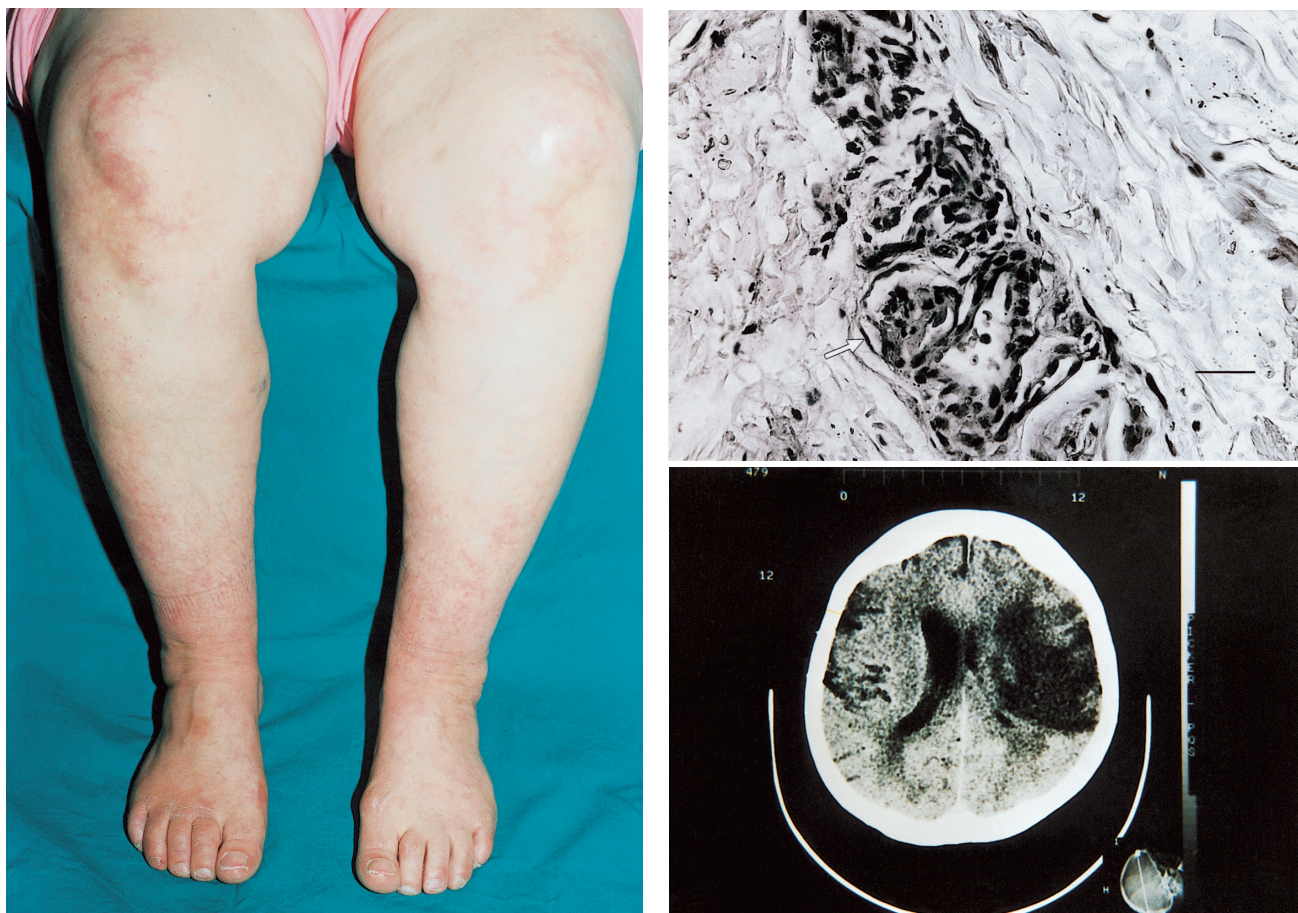


Fig. 2 A representative case (case 1). Livedo reticularis lesions are present on the lower extremities (a), thrombosed capillary veins can be seen among the ductus ekrine glands in the skin biopsy. Bar indicate $50\ \mu\text{m}$ (b), and the cranial CT scan revealed hypodense areas localized to the left middle cerebral arterial region (c).

reticularis and stroke were present in all cases. Our cranial CT analyses revealed, 4 cases with a focal hypodense area, and 3 cases with a multiple infarct area. There were capillar skin thrombosis in skin biopsies of 4 cases, migraine in 3 cases, and a history of hypertension in 4 cases.

Livedo reticularis occurs as a result of focal and persistent impairment of peripheral blood flow caused by occlusions of small arteries in cases of vasculitides or SS [5, 13]. Skin lesions in the form of livedo reticularis were seen in all of the present cases, and skin biopsy revealed thrombosed capillary veins in only 4 cases. Wohlrab *et al.* [24] presented a new biopsy technique of high sensitivity for histological investigation of the skin in SS, in which three 4-mm punch biopsies are taken from the suspected centre and 2 additional deep 4-mm punch

biopsies are taken from the livid periphery of the lesion.

It has been suggested that the occurrence of epileptic seizures in patients with SS might be due to encephalopathic changes and impairment of cerebral white matter [12, 25]. In the present study, epileptic attacks could be seen in the advanced period of the disease. Several serial studies have also reported epileptic attacks in patients with SS [2, 5, 23]. In addition, SS is one of the rare disorders causing neuroophthalmologic symptoms. Monocular and binocular ischemia and central retinal artery occlusions have also been reported in some cases of this syndrome. Rehany *et al.* presented a young patient with internuclear opthalmoplegia, followed by ophthalmic artery occlusion with SS [6, 26, 27]. The presence of epileptic seizures was supported by EEG in 2 cases and flow pattern disturbances in ophthalmic artery

Table 1 The findings of all the cases are summarized

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10
Abortus	Infertility	+	Unmarried	+	+	Infertility	+	+	+	+
Age/sex	29 f	30 f	31 f	37 f	46 f	26 f	40 f	44 f	49 f	30 f
APL	+	+	+	—	—	+	—	—	+	+
AntithrombinIII	N	↑	↑	N	N	N	N	↓	N	N
Chromosome..	N	N	N	N	N	N	N	N	N	N
Cigarette	+	—	+	—	—	—	—	—	—	+
EEG	N	Abnormal	Abnormal	N	N	N	N	N	N	N
Epilepsia	—	GTCS	focal	—	—	—	—	—	—	—
Hypertension	—	—	—	—	—	+	—	+	+	+
Inheritance	—	—	—	—	—	AD	—	—	AD	AD
L.R	+	+	+	+	+	+	+	+	+	+
MG	+	—	—	—	—	—	—	—	—	—
MI	—	—	—	+	—	—	—	+	—	—
Migraine	+	—	—	+	—	—	+	—	—	—
MRI/CT	Infarct	Infarct	Infarct	N	Infarct	Infarct	N	Infarct	Infarct	N
Organisity tests	N	N	N	N	N	Abnormal	N	N	Abnormal	N
Psychiatric..	Depression	N	N	Depression	Depression	N	N	N	N	N
Skin biopsy	+	—	—	—	—	—	+	+	+	—
Stroke	Hemiplegia	Dysphasia	Hemiplegia	Hemiplegia	Hemiplegia	Hemiplegia	A. fugax	Dysphasia	Hemiplegia	Hemiplegia
USG	N	N	N	Low	N	N	Low	N	Low	N
Visual exam	N	Hemianopia	N	N	N	N	Hemianopia	N	N	N
WIT	N	N	N	N	N	IQ: 64	N	N	IQ: 66	N

+, present; —, not present; ↑, above; ↓, below; AD, autosomal dominant; aPL, antiphospholipid antibodies; Chromosome.., chromosome analysis; EEG, electroencephalography; F, female; GTCS, generalized tonic clonic seizures; LR, livedo reticularis; MG, myasthenia gravis; MI, mitral insufficiency; MRI/CT, magnetic resonance imaging / computed tomography; N, normal; Psychiatric.., psychiatric examination; USG, ultrasonography (carotid/ ocular); Visual exam., visual examination; WIT, wechsler intelligence test.

ultrasonography in 3 cases, 2 of which showed inferior altitudinal hemianopia, indicating that vascular involvement may be generalized in SS.

It has been reported that SS is related with vascular dementia which develops as a result of chronic and recurrent stroke attacks [5]. Because of these features, SS either leads to depression as an important stress source or to neurocognitive function disturbances. In the present study, the detection of depression in 3 cases and the presence of disturbance in the visual motor perception test and mild mental retardation in 2 cases would seem to support this feature of disease. However, patients with SS can develop dementia without antecedent clinical stroke, although the specific pathogenetic mechanism of this development remains unknown [28].

Presence of antiphospholipid antibodies is in the rate of 59%, history of abortus is present in most of the women, cardiac disorders especially mitral valve disorders were all reported in SS cases [9, 14]. It has also 1 been reported that familial insufficiency of antithrombin III is related with SS [15], and qualitative insufficiency

of antithrombin III might play a role in the pathogenesis of SS [16]. Kalashnikova *et al.* measured the levels of antiprothrombin antibodies (aPT) in SS patients. The levels of aPT were elevated in 57% of patients. The addition of aPT data increased the proportion of SS patients with at least one type of antiphospholipid syndrome marker from 65% to 78% [29]. In the present study, 6 of 10 cases were positive for antiphospholipid antibodies. Antithrombin III levels were high in 2 cases, and low in 1 case. There was mitral insufficiency in 1 case, and a history of at least one abortion in seven cases.

Genetic factors should also be taken into consideration in the pathogenesis of SS, which may be related to with an antigenic stimulus against a genetic entity. SS cases with an autosomal trait have been reported [17, 28]. In addition, in diseases such as MG, migraine, Guillain-Barre Syndrome, and dementia, in which genetic and autoimmune disorders are seen together, significant positivity of phospholipid antibodies only seen at the rate of thought to occur at a rate of approximately 1-2% in the general population have been reported [17, 30-32].

There are some studies in migraine type headache, multiple sclerosis which have relation to chromosome 6 with HLA gene [17, 19, 31-34]. In addition, in some studies, SS cases with autosomal recessive transitive and autosomal dominant traits have been reported [5, 27]. In consideration of all of the above genetic factors, we produced a family tree for the present cohort.

Although the results of our analysis of chromosome 6, where the HLA gene is localized, were normal in all of the cases, the presence of an autosomal dominant trait in 3 cases, of MG in 1 case, migraine-type headache with aura in 3 cases, and of antiphospholipid antibody in 60% of the cases support the idea that SS may be accompanied with other neurological diseases from an autoimmune and genetic point of view.

Our findings indicate that Sneddon's syndrome should be followed and studied in future multidisciplinary studies, and that further studies should also be conducted to clarify the pathogenesis of this disease, particularly from a genetic point of view.

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