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CLINICAL, NEUROVASCULAR AND NEUROPATHOLOGICAL FEATURES IN SNEDDON´S SYNDROME

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ABSTRACT - Sneddon's syndrome (SS) is characterized by ischemic cerebrovascular episodes and livedo reticularis. It is more common in young women and can also be associated with valvulopathy, a history of spontaneous abortion, renal involvement and vascular dementia. We describe three cases of young women with this disease. The patients had repeated ischemic cerebral episodes, livedo reticularis and thrombocytopenia. CT and MRI showed strokes and cerebral atrophy. Autopsy in one of the patients revealed cerebral infarctions. Anticardiolipin antibodies were detected in two patients. Antiphospholipid antibodies may be found in some patients with ischemic cerebrovascular events and livedo reticularis. SS may thus be associated with antiphospholipid syndrome. We described three new cases of SS and discuss the pathophysiology of this disease.

KEY WORDS: antiphospholipid syndrome, cerebrovascular diseases, neuroimaging, neuropathology, Sneddon's syndrome.

Características clínicas, neurovasculares e neuropatológicas na síndrome de Sneddon

RESUMO - A síndrome de Sneddon é caracterizada por episódios cerebrovasculares isquêmicos e livedo reticular, sendo mais comum em mulheres jovens, e pode também apresentar valvulopatia, história de aborto, envolvimento renal e demência vascular. Descrevemos três mulheres jovens com esta entidade. Os pacientes apresentavam história de ataques isquêmicos cerebrais, livedo reticular e trombocitopenia. Tomografia computadorizada e ressonância magnética de crânio mostraram infartos e atrofia cerebral nos pacientes estudados. A autópsia revelou em um dos pacientes presença de infartos cerebrais. Anticorpos anticardiolipina foram observados em duas pacientes. Há pacientes com eventos cerebrovasculares isquêmicos e livedo reticular nos quais anticorpos antifosfolípides são detectados. Então SS pode estar associada com a síndrome antifosfolípide, porém em alguns pacientes estes anticorpos não são detectados. Nós descrevemos três novos casos de SS e discutimos os mecanismos fisiopatológicos desta síndrome.

PALAVRAS-CHAVE: doenças cerebrovasculares, neuroimagem, neuropatologia, síndrome antifosfolípide, síndrome de Sneddon.

Sneddon´s syndrome (SS) is characterized by the combination of ischemic cerebrovascular episodes and a widespread livedoid eruption. Although this association was first described in a patient in 1960 by Champion and Rook[1], only later, in 1965, did Sneddon suggest this association in six new cases[2]. SS is more common in women between 20 and 42 years of age[3] and can be accompanied by other manifestations such as systemic hypertension, acrocyanosis, Raynaud's phenomenon[4], secondary headaches[3-5], venous thrombosis[4], valvulopathy[4], a history of spontaneous abortions[3,6], seizures[3,7], renal involvement[8], and vascular dementia[9,10]. Antiphospholipid antibodies can also be found at a highly variable frequency[3,4,11].

The frequency of headache is not significantly higher in persons with positive anti-phospholipid antibodies compared with the negative cohort (43% vs. 32%), with a female to male ratio of 3.5:1. The association with SS and primary headaches, such as mi-

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graine occurs in 27.5% of the cases when SS is followed of headache[12]. Livedo reticularis often precedes the cerebrovascular events, whose onset usually occurs before the age of 45 years. These events consist of ischemic strokes or transient ischemic attacks, which affect mainly medium-sized arteries and are seen particularly in the territory of the middle and posterior cerebral artery[4,5,13-15]. Intracerebral, subarachnoid or intraventricular hemorrhages have also been reported[16,17].

In this paper we describe three cases of Sneddon's syndrome including clinical, neuroimaging and neuropathological features.

METHOD

The cases were followed up in the Neurology Division of the Hospital das Clínicas of Federal University of Paraná (UFPR) from 1992 to 2006. The patients underwent clinical and neurological examination (Table 1). Extensive laboratory analysis was performed. Echocardiography, transcranial doppler, cranial computed tomography (CT), magnetic resonance imaging of the brain (MRI) and cerebral angiography were also carried out. Diagnosis was based on the presence of livedo reticularis and ischemic cerebral events, as evidenced by clinical history, neurological and clinical examination and neuroimaging tests. In the first patient this was also evidenced by autopsy, which included macroscopic and microscopic analysis. The sections were stained with hematoxylin and eosin (H&E) and other routine stains. The limitation of this study is that we did not determine the factor V of Leiden mutations in our patients.

All subjects, or family of them, provided written informed consent, as required by appropriate local (and national) committees on the protection of research subjects.

Cases

Case 1 – A 24-year-old woman with a history of epilepsy and repeated strokes, of which the first at the age of 18 years, was referred to the Neurology Division of the Hospital das Clínicas (UFPR) for study. Five years later her first stroke, the patient had a new episode and was admitted to hospital with right hemiplegia, right-central fa-

Table 1. Clinical and epidemiological features of three cases of Sneddon's syndrome.

Clinical features	Case # 1	Case # 2	Case # 3
Gender	Female	Female	Female
Age	24 years	29 years	42 years
Previous stroke	First at 18 years	First at 29 years	Yes
History of livedo	Since childhood	+	+
History of spontaneous abortion	One	Two	One
History of smoking	–	+	+

(+) yes, (–) no.

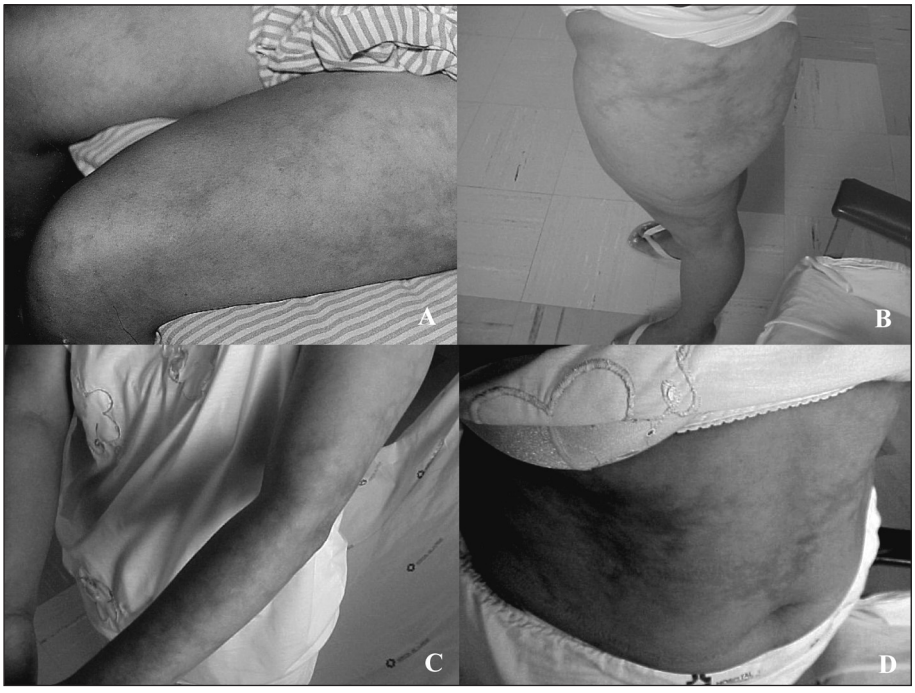

Fig 1. Skin showing livedo reticularis on the lower extremities in patient number one (A) and on different parts of the body in patient number three (B, C, D).

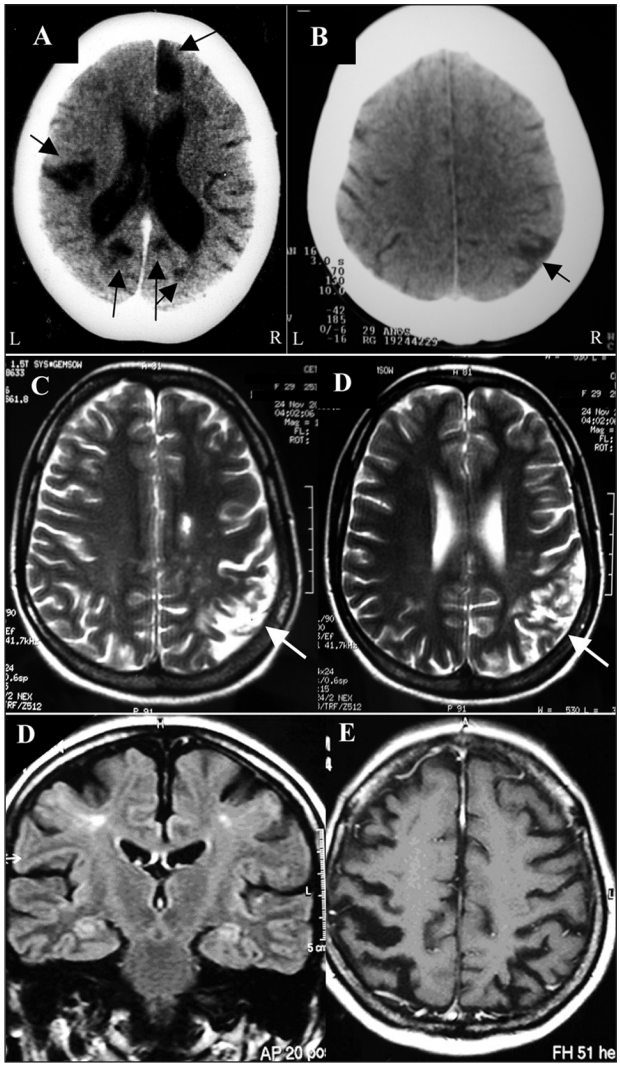

Fig 2. Cranial CT showing volumetric reduction of the cerebral hemispherium and hypodense areas in the right-temporal, left-frontal and bilateral occipital regions compatible with infarctions (arrows) in patient number one (A) and an area of cerebral infarction in the left parietal region (arrows) in patient number two (B). T2-weighted MRI showing area in keeping with cranial CT (arrows) in patient number two (C) and cerebral atrophy with anomalous signals in the subcortical white matter in patient number three in coronal (D) and axial sections (E).

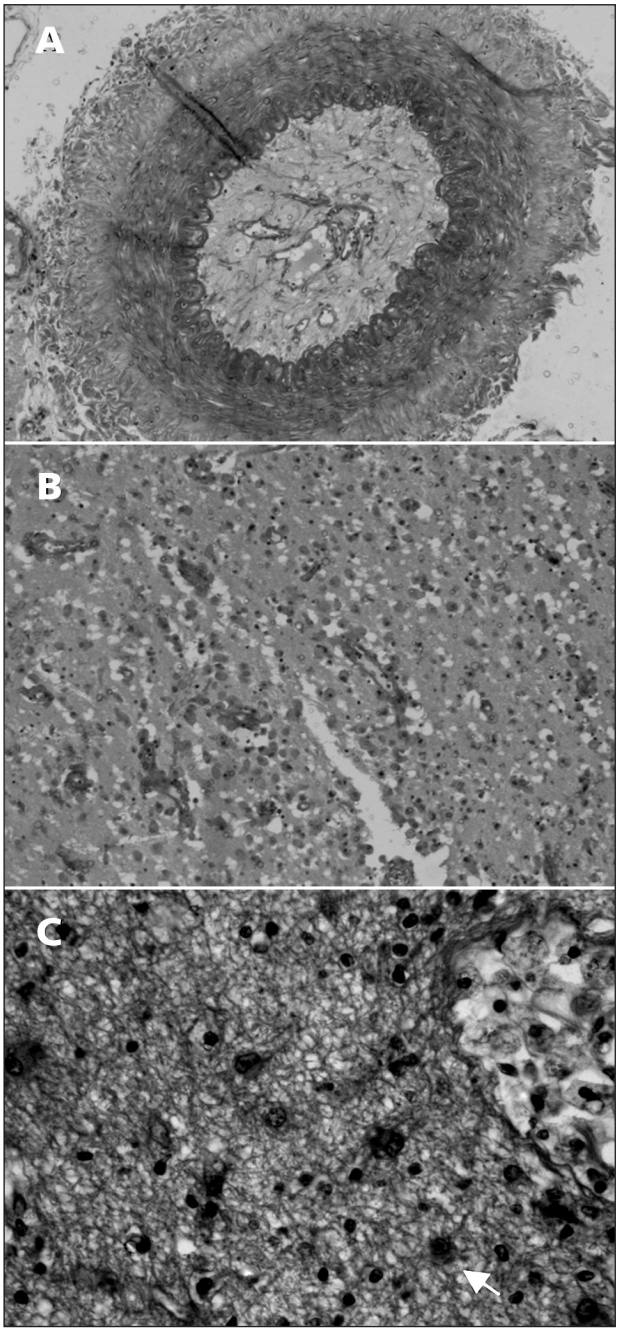

Fig 3. Cerebral microscopy in patient number one shows organized thrombosis in small and medium-caliber arteries with recanalization (H&E, original magnification: x100) (A); areas of recent infarction with alteration of the usual staining characteristics, liquefactive necrosis and lipid-laden histiocytes (H&E, original magnification: x100) (B); and areas of old infarctions with gliosis and a large number of gemistocytic astrocytes (arrow) (H&E, original magnification: x400) (C).

cial palsy, aphasia and dysphagia. Livedo reticularis was observed, particularly on the arms and legs (Fig 1A). Cranial CT showed ischemic strokes (Fig 2A). Acetylsalicylic acid was maintained, and treatment with corticoids, oral anticoagulants and anti-hypertensive agents was introduced. The patient was discharged from hospital with a diagnosis of Sneddon´s syndrome.

Four weeks later the patient started to develop holocranial headache followed by decreased consciousness. Her blood pressure was 170/110 mmHg at admission. The neurological examination showed mental confusion, dysphasia, dysphagia, left facial paralysis with crural paraparesis, spasticity on the right side, bilateral extensor plantar response, generalized hyperreflexia and bilateral Hoffmann's sign. The results of cranial CT and blood tests are shown in Tables 2 and 3.

On the eleventh and twenty-first days after hospitalization, the patient developed urinary bleeding, epistaxis and

Table 2. Blood tests of three patients with Sneddon's syndrome.

Tests	Case # 1	Case # 2	Case # 3
Anticardiolipin antibodies	Negative	IgG 13.1 GPL IgM 22.4 MPL	IgG negative IgM 11.7 MPL
Lupus anticoagulant	Negative	Negative	Slightly positive
VDRL	Negative	1:4	Negative
FTA-Abs	–	IgG and IgM negative	–
Antinuclear factor	Negative	1:160 (multiple nuclear dot pattern)	Negative
Anti-DNA antibody	Negative	–	Negative
Anti-SM/anti-RNP/Anti-La and anti-Ro antibodies	–	Negative	–
Rheumatoid factor	–	Normal	–
LE cells	Negative	Negative	–
Platelet count	18,000-36,000	17,000-64,000	150,000
C and S proteins	–	–	C protein normal S protein 185% (VR 70-123%)
Antithrombine III	–	–	Normal
C3-C4-CH50	Normal	Normal	Normal
HIV serology	Negative	Negative	Negative
Cytomegalovirus, listeria and toxoplasmosis serology	Negative	Negative	–
Hepatitis B and C serology	–	Negative	–
Lactic acid	Normal	Normal	–
Thyroid function	Normal	Normal	–
C-reactive protein	–	Normal	Normal
Blood sedimentation rate	–	Normal	Normal
Cerebrospinal fluid	Normal	Normal	Normal

Table 3. Neuroradiologic and pathological features of three patients with Sneddon's syndrome.

Tests	Case # 1	Case # 2	Case # 3
Cranial CT	Hypodense areas in right temporal, left parietal and bilateral occipital regions (at 18 years of age); also volumetric reduction of cerebral hemispherium (at 27 years of age)	Prominent sulci in left parietal region suggestive of sequel, and a small right parietal calcification	Cerebral atrophy
Arteriography	Occlusions in rami of left middle cerebral artery	–	Distal slowness of reduced-caliber cerebral arteries and parietal irregularity suggestive of vasculitis
Brain MRI	–	Hyperintense signals on T2-weighted and FLAIR images in cortical and subcortical regions of the left parietal lobe	Cerebral atrophy with anomalous signals in the subcortical white substance
Echocardiography	Normal	Slightly thick extremity of anterior mitral-valve leaflet	Left ventricular hypertrophy with mitral valve stenosis
Vascular ultrasonography of carotid and vertebral arteries	Normal	Normal	Normal
Transcranial doppler	Normal	Compensatory vasodilatation of right middle and anterior cerebral arteries	–

upper digestive hemorrhage followed by hypotension. On the fifty-third day the patient had subconjunctival haemorrhage, ecchymosis on the arms, legs and trunk, and massive proteinuria. Two days later the patient had alternate periods of apathy and psychomotor agitation. The following day, despite the treatment, she progressed to shock followed by death.

The post-mortem examination revealed recent cerebral infarctions located in the left frontal pole (measuring 4 x 4 x 4 cm), the right-anterior cerebral-artery territory (5 x 4 x 2 cm) and the right hippocampus. There were also old cerebral infarctions in the left-anterior cerebral-artery territory and in the temporal, occipital and insular regions. Cerebral sulci and ventriculi were enlarged, but the cerebral gyri were narrowed. No areas of hemorrhage were found. The cerebellum and brainstem had no abnormalities. Microscopy also showed important cerebral alterations (Fig 3). Acute thrombotic non-infectious endocarditis of the mitral valve with fibrosis, suggesting a recurrent process, as well as pericardial effusion (200 mL) and cardiac ventricular hypertrophy (heart weight, 350 g) were found. Membranoproliferative glomerulonephropathy with hyaline tubular vacuolar degeneration and hyaline casts as well as mild renal arteriolosclerosis with old infarctions and acute hemorrhagic cystitis were also observed.

Case 2 – A 29-year-old woman was referred with right hemiplegia, and hemiparesthesia. Two years before the stroke, the patient presented thrombocytopenia (50,000 platelets/μL) and a history of two spontaneous abortions. Although she used prednisone for six months, platelet count did not increase. Clinical examination showed livedo reticularis, Raynaud's phenomenon and muscle strength grade IV on the right side. The results of blood and neuroradiologic tests are shown in Tables 2 and 3 and Figs 2B and 2C.

Heparin was replaced by oral anticoagulant, but the patient continues to suffer from thrombocytopenia and is being assisted in the outpatient ward.

Case 3 – A 42-year-old woman with a history of epilepsy and two stroke events was admitted to the Neurology Division for investigation. At admission the patient presented with right hemiparesis, right hemiparesthesia and secondary headache. The patient had a history of spontaneous abortion and hypertension and had taken carbamazepine 200 mg tid, phenytoin 300 mg qd, asperin 100 mg qd and captopril 25 mg bid. Clinical examination revealed livedo reticularis (Figs 1B, 1C and 1D), Raynaud's phenomenon and reduced muscle strength on the right side. Blood and neuroradiologic tests are shown in Tables 2 and 3 and Figs 2D and 2E.

DISCUSSION

Patients with ischemic cerebrovascular events, livedo reticularis and antiphospholipid antibodies are considered by some authors to have primary antiphospholipid syndrome[6,18-20] while for other authors these antibodies are involved in the pathogenesis of Sneddon´s syndrome[3]. Studies of patients with Sneddon's syndrome revealed elevated antiphospholipid-antibody levels in 57% of patients matched with normal controls[11]. However, in some patients these antibodies are repeatedly not found[20,21], indicating that Sneddon's syndrome may be a distinct entity or perhaps a group of different disorders[14] because there are clinical differences in patients with or without antiphospholipid antibodies[4,6,22]. It is essential to keep this point in mind, as some important clinical features that are described in patients with Sneddon's syndrome are found in patients with primary antiphospholipid syndrome or systemic lupus erythematosus[4,23].

According to Francès and Piette[4], thrombocytopenia is a common feature of primary antiphospholipid syndrome and of Sneddon´s syndrome in patients with antiphospholipid antibodies, but is not a feature of cases in which these antibodies are not found. This could explain the persistent thrombocytopenia observed in the second patient, as thrombocytopenia, livedo reticularis and stroke are described in a large number of patients with antiphospholipid syndrome[23,24-26]. However, venous thrombosis was not found in these three patients although it is an important feature of antiphospholipid syndrome[23,26].

The first and third patients had cerebral atrophy, which is described in Sneddon's syndrome as a progressive complication due to involvement of small arteries[20]. Nonetheless, in primary antiphospholipid syndrome the neurological findings are stable because the affected arteries are larger than those affected in Sneddon's syndrome[20]. However, the absence of cerebral atrophy in the second patient does not exclude a diagnosis of Sneddon's syndrome.

Other features described in Sneddon's syndrome[3,4,6-8] were also found in these three patients and contributed to the diagnosis; these included hypertension, renal and cardiac disorders, Raynaud's phenomenon, seizures and a history of spontaneous abortions. The first patient had livedo reticularis and seizures for the first time during her childhood, as described in Sneddon's syndrome[3,7].

Although the pathogenesis of Sneddon's syndrome with the presence of antiphospholipid antibodies may be explained in a similar manner to the pathogenesis of antiphospholipid syndrome[27-30], the significance of the presence of these antibodies in both syndromes is unclear[31,32].

These three cases illustrate the importance and

severity of Sneddon's syndrome as well as the importance of the differential diagnosis of ischemic cerebrovascular events in young patients, particularly in cases where antiphospholipid antibodies cannot be detected.

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