SNEDDON SYNDROME: RARE DISEASE OR UNDER DIAGNOSED CLINICAL ENTITY? REVIEW OF THE LITERATURE RELATED TO A CLINICAL CASE

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SNEDDON SYNDROME: RARE DISEASE OR UNDER DIAGNOSED CLINICAL ENTITY? REVIEW OF THE LITERATURE RELATED TO A CLINICAL CASE (Abstract). Sneddon syndrome is defined by the association of livedo racemosa and recurrent cerebrovascular ischemic lesions. The annual incidence is 4/1,000,000. This syndrome particularly affects young women, some reports suggesting a family predisposition. It is a chronic, progressive, arterio-occlusive disease of unknown etiology that involves small and medium-sized arteries. It is usually associated with antiphospholipid antibodies. We report the case of a female patient with Sneddon syndrome with significant family history, personal history of stroke, epilepsy, migraine, cardiovascular involvement, three miscarriages, cognitive decline, noncompliant to therapy, in the absence of antiphospholipid antibodies. This paper aims to analyze the main characteristic features and management of Sneddon syndrome by conducting a literature review related to a clinical case. Keywords: SNEDDON SYNDROME, CEREBROVASCULAR DISORDER, LIVEDO RACEMOSA, ANTI-PHOSPHOLIPID ANTIBODIES.

Sneddon syndrome is a condition characterized by the association of livedo racemosa and ischemic strokes (especially in the middle cerebral artery territory); it was named after the British dermatologist Sneddon, the first to draw attention to this association in 1965. Sneddon syndrome affects mainly women (80%) aged 20-40 years; livedo racemosa precedes neurologic impairment and the first cerebral ischemic event usually occurs before the age of 45.

The annual incidence is estimated at 4/1,000,000 but data suggest that Sneddon syndrome is under diagnosed; it has been estimated that Sneddon syndrome affects 1:2000 stroke patients and the prognosis for these patients is poor (1).

It is a chronic, progressive, non-inflammatory, arterial occlusive disease of unknown cause that affects small and medium sized arteries in the brain and skin, although there are studies that state its system-
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Cardiovascular system is the most commonly involved (hypertension, ischemic heart disease, valvular disease), but the visual system, gastro-intestinal system and kidneys may also be affected. The association with antiphospho-lipid antibodies is controversial (0-85%).

Some studies describe a significant family history in Sneddon syndrome patients, and autosomal dominant with incomplete penetrance or autosomal recessive arrays were suggested (2, 3, 4).

Sneddon syndrome is not currently regarded only as a clinical diagnosis but rather as a common clinical manifestation of different diseases. Various authors have classified the disorder in primary Sneddon syndrome (without evidence of etiological factors) and secondary (autoimmune, thromboembolic, associated with systemic lupus erythematosus, associated with antiphospholipid syndrome) (5). No treatment has proven effective for this condition.

Pathophysiology. Recent data suggest that Sneddon syndrome begins as an inflammatory, possibly immunologically-mediated disorder which develops into the migration and proliferation of smooth muscle cells in small and medium-sized arteries that result in vessel stenosis. The disease progresses in four stages: early stage (I), characterized by attachment of lymphohistiocytic cells and detachment of endothelial cells followed in stage II by total or partial occlusion of the lumen with a plug of fibrin and lymphohistiocytic cells; the plug is then replaced in stage III by proliferating subendothelial cells and stage IV is characterized by fibrosis and stenosis of the vessel (1,6).

Clinical diagnosis. Sneddon syndrome is a clinical diagnosis as there is still no specific test for it. Livedo racemosa is usually located on the limbs (100%), trunk (89%), buttocks (74%), face (15%), hands and feet (59%). Neurological manifestations occur after an ischemic stroke, usually in the middle cerebral artery territory and usually consist of hemiparesis, sensory deficits, aphasia and dysarthria, but visual field deficits and drop attacks may also occur. TIAs are common and spinal infarcts, intracerebral, subarachnoid and intraventricular hemorrhages were also reported (1).

Other neurological manifestations associated with Sneddon syndrome are headache, vertigo (the most common), chorea, epilepsy, myelopathy, migraine, hemi-crania, acute encephalopathy, amnesia, internuclear ophthalmoplegia, nystag-mus, ophthalmic artery occlusion, myasthenia gravis, polynuropathy, Raynaud syndrome (1). In almost all cases the disease advances to cognitive dysfunction, personality changes, depression and late dementia.

Impairment of other systems has been reported: cardiovascular (hypertension, valvular, aortic or mitral regurgitation usually, ischemic heart disease), ocular, gastrointestinal, renal, gynecological (miscarriages, sterility), suggesting a systemic nature of the disease (1, 7, 8).

Of the clinical manifestations, migraine and headache appear to be most strongly associated with the risk of a new stroke (9).

Laboratory exams. Recent studies support the importance of skin biopsy and cranial imaging in the diagnosis of Sneddon syndrome. Wohlrab et al. used a skin biopsy method that required taking a deep punch biopsy (4 mm) from the white areas, the sensitivity of the method increasing with the number of biopsies: 27% one biopsy, 53% two biopsies, and 80% with three biopsies (10). Ultrastructural and immunohistochemical investigations have shown that the migrating cells from the media contain smooth muscle actin (smooth muscle cells or myofi-
broblastic cells). Hilton and Footitt reported the main findings in the brain tissue biopsy to be small cortical infarcts associated with the occlusion of the small and medium arteries and prominent focal hyperplasia of the media in the small arteries, similar to the skin findings (1).

MRI can detect cortical and/or subcortical arterial infarcts, usually multiple, and periventricular white matter abnormalities. Diffuse cortical-subcortical atrophy has been reported in advanced stages. The results of cranial angiography are inconsistent, some studies describing various abnormalities (irregular vessel calibre, occlusion or stenosis of major cerebral vessels, medium and small vessel stenosis, large networks of fine collateral vessels and granulomatous leptomeningeal infiltra-
tion, transdural anastomoses, lobar intracerebral hemorrhage with “pseudo-
angiomatosis” pattern), others did not report any abnormalities (1,11).

Stockhammer suggested using MRI and duplex sonography in detecting large vessel occlusions, while Canepari et al. have demonstrated a strong relation between SPECT analysis of cerebral perfusion, clinical findings, and disease progression; functional imaging associated with MRI seem to have a good sensitivity in the follow-up of these patients (11, 12, 13).

The combination of Sneddon syndrome and antiphospholipid antibodies (APAs) has been reported in quite variable percentage, ranging from 0 to 85%, most authors suggesting values of 40-50% (1). Some authors have concluded that thrombocyto-
penia, proteinuria, epilepsy, and mitral regurgitation occur more often in the presence of APAs associated with Sneddon syndrome, whereas livedo network appears to be broader in Sneddon syndrome without APAs. Others have found that the presence of APAs indicates a lower risk of throm-
bosis and a much less severe course of the disease (1, 14, 15).

Numerous other prothrombotic abnormalities have been reported: heterozygous factor V Leiden mutation, deficiency of protein Z, resistance to activated protein C, increased platelet aggregation, and increased β-tromboglobulin, modified plasminogen activator/inhibitor ratio, familial antithrombin III deficiency, increased factor VII activity (1, 16, 17, 18, 19). Our patient tested negative for APAs, proteins C and S were normal, although bleeding and clotting parameters were modified.

**Differential diagnosis.** Differential diagnoses include other conditions that associate livedo racemosa and cerebrovascular events such as: APA, systemic lupus ery-thematosus (SLE)- it can present with live-
do racemosa (11.7%), especially associated with anti-Ro antibodies, and neurological symptoms (amnesia, cognitive impairement, depression), Divry van Bogaert syndrome, thrombangiitis obliterans - reported as a rare complication of Buerger disease, is clinically similar to Sneddon syndrome.

Other differential diagnoses to be con-
sidered are polyarteritis nodosa, cholesterol emboli syndrome, livedoid vasculopathy. Rarely, livedo racemosa may be associated with: hematological abnormalities (essential thrombocytemia, polycythemia vera, perni-
cious anemia, DIC, cryofibrino-genemia), hyperthyroidism, rheumatoid arthritis, Sjogren's syndrome, derma-
tomyositis, scleroderma, temporal arteritis, calciphylaxis in chronic dialysis patients, hyperoxaluria, atrial myxoma, post-streptococcal syn-
drome, borreliosis (1).

**Course.** The natural course of Sneddon syndrome is marked by recurrent ischemic strokes accompanied by progressive cere-
bral atrophy and dementia, leading to disa-
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bility and a mortality of 9.5% over an observation period of 6.2 years (11).

Treatment. Due to lack of controlled trials, the management of Sneddon syndrome patients remains controversial. Corticosteroids and immunosuppressive therapy appear to be ineffective. It has been found that the presence of APAs in Sneddon syndrome may influence the management and patients with positive APA respond well to anticoagulant treatment with warfarin in high doses (20). Wohlrab et al. proposed a long-term triple prophylactic therapy with pro-rheological agents (prostaglandin E1), against myocyte proliferation (Captopril) and antiplatelet that led to halting disease progression over 3-5 years (1). Hannon et al. reported improved memory and emotional status after treatment with cyclophosphamide (21), while other authors state that intravenous thrombolysis may be effective and safe in patients with Sneddon syndrome (22); also, these patients should avoid smoking and oral estrogen contraceptives (1).

Prognosis. It seems that patients who associate APAs have a better prognosis than those without APAs, and a better response to anticoagulant treatment. Systemic involvement, especially cardiovascular, leads to a poorer prognosis and the presence of migraine in patients with Sneddon syndrome is associated with an increased risk of stroke (9, 10). The best follow-up methods for preventing cerebrovascular ischemic lesions in patients with Sneddon syndrome seem to be the brain imaging techniques (MRI and SPECT) (13).

Although Sneddon syndrome is a clinical diagnosis, it requires multiple investigations, necessary for initial assessment of systemic involvement, prognosis and treatment plan.

CASE PRESENTATION

To illustrate the complexity of approaching such a patient we present the case of a 42-year-old woman admitted to the Department of Internal Medicine of the Iasi "Dr. C.I. Parhon" Hospital who upon admission showed uncontrolled high blood pressure values, frontal occipital headache of moderate intensity (5 p/10 on the visual analog scale), faintness, vertigo accompanied by nausea and vomiting, visual disturbances, muscle weakness and chest pain.

Physical exam revealed skin changes characteristic for "livedo racemosa" (fig. 1, 2), visible on the thighs, arms and trunk, with onset at the age of 22 years and

Fig. 1. Livedo racemosa of the left arm

Fig. 2. Livedo racemosa of the legs
trophic disorders of the legs.

Neurological exam revealed left spastic hemiparesis, left facial paresis, central motor deficit of the left limbs.

Our patient had a significant family history, a grandmother who died of stroke, a brother who suffered from stroke, the mother who had livedo reticularis and a personal history of three miscarriages, grade 3 arterial hypertension, epilepsy and migraine.

Known with neglected arterial hypertension, nonsmoker, denied use of estrogen products, our patient presented an episode of left faciobrachial motor deficit resolved within 3-4 days at the age of 34. At the age of 39 she suddenly experienced a left limb motor deficit following strenuous exercise; glucocorticoids and antiplatelet agents were administrated and the course was favorable.

The suspicion diagnoses were Sneddon syndrome, antiphospholipid antibody syndrome, and systemic lupus erythematosus; for confirming the diagnosis we performed full blood and biochemical tests, autoimmune markers, coagulation tests, heart examination (ECG, Holter, transthoracic echocardiography), CT, MRI and skin biopsy and the results were:

- Brain MRI: multiple ischemic brain lesions located in the right parietal and left occipital lobes (fig. 3) while cranial CT showed an insular frontal ischemic sequel and cerebral atrophy;
- Laboratory tests: the absence of antiphospholipid antibodies, p-ANCA and c-ANCA, ANA and anti-dsDNA antibodies were negative, protein C and S were normal, while bleeding and coagulation time were decreased (BT = 1'00", CT = 5'48");
- Skin biopsy: discreet perivascular lymphocytic infiltrate and bulging of vascular endothelium;
- Holter: systolic values ranged between 140-160 mm/Hg and echocardiography revealed normal heart cavities, with a LVEF = 65%.

Fig. 3. MRI imaging: Ischemic lesions located in the right parietal and left occipital lobe

In our patient, a positive diagnosis of Sneddon syndrome was based on the presence of clinical symptoms (livedo racemosa, neurological and cognitive impairment), history of stroke, and brain imaging suggestive of ischemic changes accompanied by cerebral atrophy.

The most efficient and used drugs for arterial hypertension associated with angina pectoris seems to be ß blockers and angiotensin receptor blockers II /sartans (23) and our pacient was treated with ß blocker, vasodilator, antiplatelet, oral anticoagulant and neurological treatment, resulting in halting the progression of the disease, with good blood pressure control and absence of a new cerebral ischemic event or degradation of cognitive status, but unchanged neurologic manifestations.

As our patient had a suggestive family history, personal history of two strokes, cognitive dysfunction (suggestive of an
advanced stage of disease), migraine, cardiovascular abnormalities (hypertension, angina pectoris), pro-thrombotic status (suggested by the 3 miscarriages), tested negative for APAs (usually associated with poor anticoagulant response and a more severe course of the disease) and was non-compliant, the prognosis was poor.

CONCLUSIONS
Although considered a rare disease, new studies show that Sneddon syndrome is actually an under diagnosed clinical entity and recognizing this disease is important in the management and subsequently in the outcome of these patients. Therapeutic conduct in these cases is difficult in the absence of a well-established protocol. Management of patients with Sneddon's syndrome should be multidisciplinary because morbidity is significant (recurrent stroke, cardiac ischemia, hypertension, miscarriages, cognitive impairment). The evolution is progressive; therefore the follow-up for these patients should be regularly done, both by clinical examination and by analyzing MRI, SPECT and echocardiography. In the absence of effective treatment, management of these patients involves removing known modifiable risk factors (smoking and eliminating estrogen products, cardiac ischemia, hypertension, hypercoagulability, epilepsy).

Our patient had multiple risk factors and was diagnosed with Sneddon syndrome 20 years after the first symptoms appeared. A more prompt diagnosis would have led to a more rapid initiation of appropriate treatment and as such to an improved prognosis.

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REFERENCES


