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Familial Sneddon's syndrome

A syndrome associating Livedo Reticularis (LR) with Cerebrovascular disease (CVD) was described, in 1965, by Sneddon. It occurs sporadically, but a few familial cases of Sneddon's Syndrome (SS) have been reported, like these 3 cases that represent one of the largest number among siblings. We studied three male brothers, aged 28, 37 and 42 years, with CVD (ischaemic stroke in 2 patients and cerebral haemorrhages in the third) and their sister with no CVD. All patients presented with long lasting Livedo Reticularis, extending beyond the lower limbs. Skin biopsy on the centre of the reticular pattern showed, only in the second patient, partial endothelium detachment in dermo-hypodermic blood vessels. The males also had accesses of Livedoid Vasculitis (LV), in which a skin biopsy showed obliteration of several upper dermal vessels with hyalin thrombi and a very scarce inflammatory infiltrate. Complementary studies, with an extensive investigation on pro-coagulation/pro-thrombotic features including antiphospholipid antibodies, were repeatedly negative. Their non-consanguineous parents were not affected, but among these kindred of 9 individuals, apart from the 4 patients reported above, LR and LV were present in two other brothers and also in an aunt and uncle, suggesting autosomal dominant pattern of inheritance, with incomplete penetrance. The relationship between Sneddon's Syndrome and Antiphospholipid Antibody Syndrome is controversial. The present cases, having repeatedly negative antiphospholipid antibodies, support the classification of Sneddon's Syndrome as an independent nosological entity.

Key words: Cerebrovascular Disease, Livedo Reticularis, Livedoid Vasculitis, Sneddon's Syndrome, Antiphospholipid Antibody Syndrome

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The association of Livedo Reticularis (LR) and cerebrovascular disease (CVD), occurring in the absence of any predisposing disease, was first described, in 1965, by Sneddon, in 6 patients, 5 of whom were women [1]. This association was further reported in more than 100 cases and is now known as Sneddon's syndrome [2-31]. It occurs sporadically, but some familial cases have been reported [2-7]. We had the opportunity to study four members of a kindred of 9 individuals all with exuberant LR, 3 of whom also had CVD.

Case Reports

Patient 1 – A 28-year-old male, with a personal history of mild hypertension, was hospitalised at the Neurology Department, in January 2000, with sudden weakness of the upper and lower right limbs due to a left ischaemic stroke. Imaging data revealed infarcted areas on MRI (*Fig. 1*). A CT scan and a cerebral angiography were normal.

Patient 2 – A 42-year-old male, also with a personal history of mild hypertension, was admitted to the Neurology Department, in February 2000, with a sudden weakness in the left limbs due to a right ischaemic stroke.

Complementary imaging data showed infarcted areas on CT scan and MRI; cerebral angiography was normal.

Patient 3 – A 38-year-old male was hospitalised at the Neurology Department, in November 2001, for re-examination after the occurrence of 2 intracerebral haemorrhages (age 23 and 34). He also had mild hypertension. Complementary imaging examination, performed then, revealed haemorrhagic areas on a CT scan and haemorrhagic sequellae on MRI; angiography was normal.

Patient 4 – A 32-year-old female sister, with no spontaneous fetal deaths, no use of oral contraceptives and no systemic hypertension, was also studied in November 2001. She had no history of cerebrovascular events and imaging data of the central nervous system showed no alterations.

None of them had a history of smoking.

Dermatological examination showed, in all patients, persistent violaceous Livedo Reticularis (*Fig. 2*), with a large, asymmetric, open reticular pattern, localised mainly in the lower limbs and buttocks, extending to the trunk and upper limbs in the 3 male patients. LR began between the ages of 13 and 18 and slowly progressed thereafter, being most striking in the third patient, whose LR began at an earlier age. Histology of a scalpel skin biopsy performed in the centre of the reticular pattern and deep into the

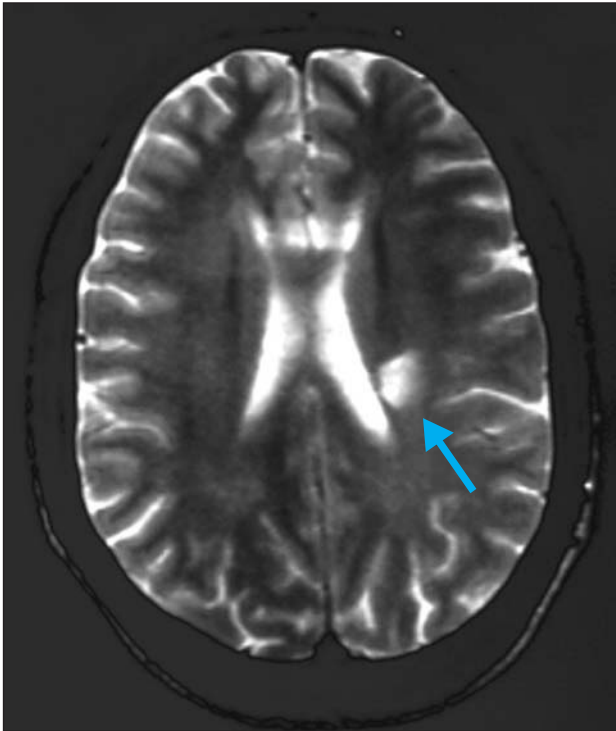


Figure 1. MRI in patient 1, showing infarcted areas.

adipose tissue revealed abnormalities only in the second patient: partial endothelium detachment in dermo-hypodermic blood vessels with no inflammatory infiltrate (Fig. 3).

In the lower legs, the three male brothers also had brownish and purpuric macules with atrophic porcelanic scars resulting from seasonal ulceration (Fig. 4). A skin biopsy performed in patient 1, in a recent necrotic lesion of the lower leg, showed hyalin thrombi obliterating several upper dermal vessels, with a very scarce inflammatory infiltrate.

Direct immunofluorescence in normal skin was negative in all patients.



Figure 2. Livedo reticularis also affecting the trunk, in patient 2.

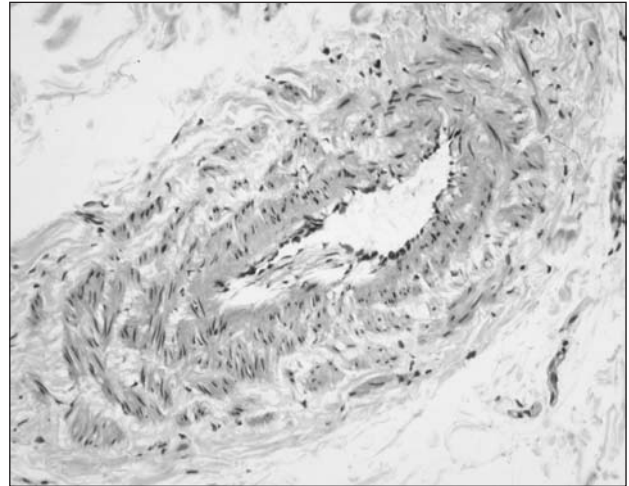


Figure 3. Histology of LR in patient 2: a detail showing partial endothelium detachment (H and E).

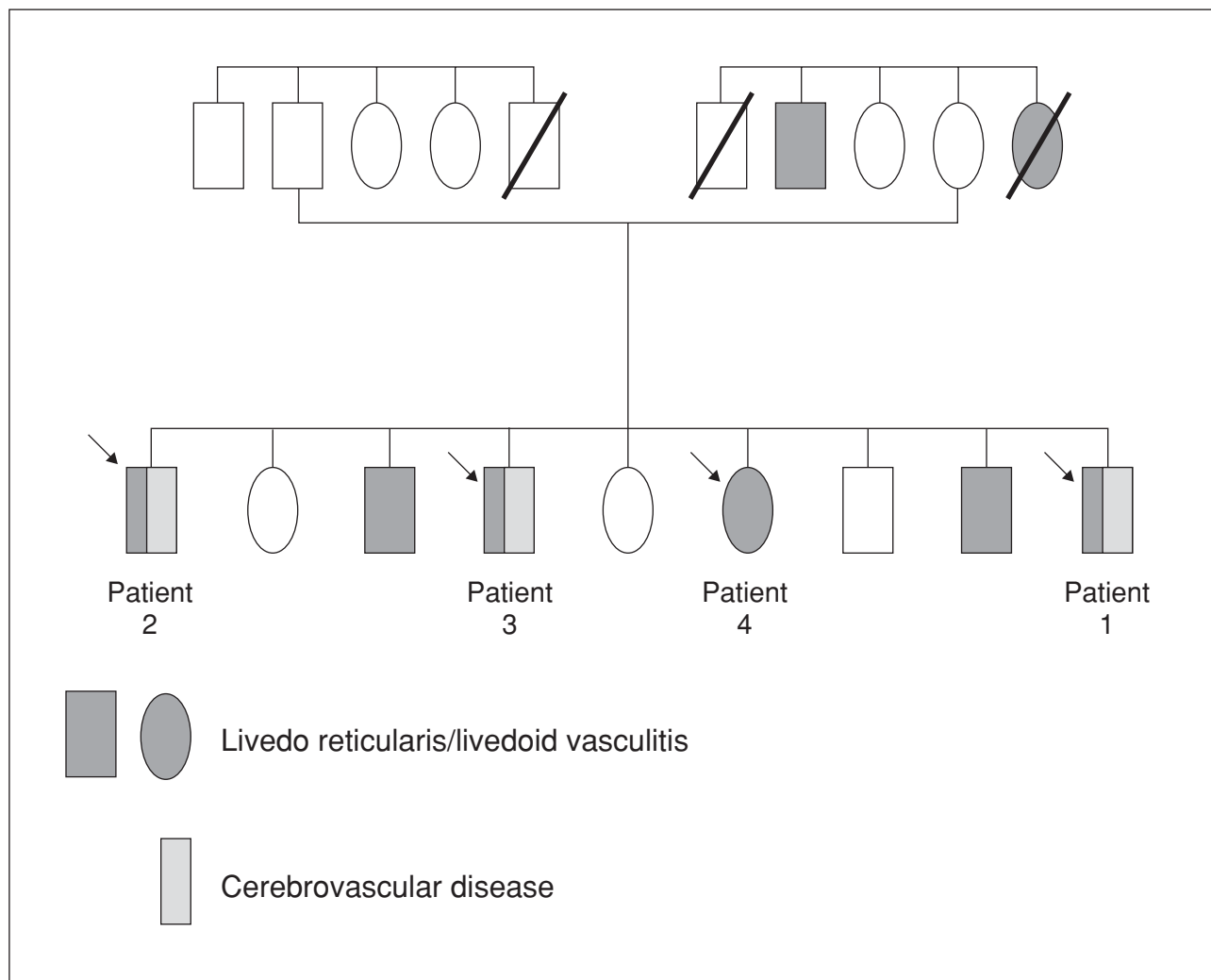
The study for cerebral stroke occurring in youth, performed at least twice in each patient, more than 6 months apart, was normal or negative. It included complete blood cell count, blood chemistry, erythrocyte sedimentation rate, lipid profile, serum protein electrophoresis, cryoglobulins, circulating immune complexes, coagulation studies, pro-thrombotic factors (antithrombin III, antiplasmin, fibrin degradation products, fibrinogen, lupus anticoagulant, C and S protein, prothrombin mutation, Factor V of Leiden, Factors II, V, VII, VIII (C/AG), IX C, X, XII, Homocysteine, MTHFR / GA 20210 II), complement fractions (C3, C4), rheumatoid factor, VDRL, anti-nuclear antibodies (ANA), antineutrophil cytoplasm antibodies (ANCA), anticardiolipine antibodies (IgG, IgM), anti- β 2GPI antibodies (IgG, IgM), antiphospholipid antibodies (IgG, IgM). Serology for HIV 1 and 2, ECG, echocardiography and carotid duplex sonography, was normal or negative.

As patients refused treatment with warfarine, they are all under treatment with an antiplatelet agent (acetylsalicylic



Figure 4. Atrophic scars resulting from seasonal accesses of livedoid vasculitis in patient 2.

Table I. Pedigree suggesting a dominant autosomal transmission with incomplete penetrance and variable expressivity



acid, 150 mg, daily), associated with antithrombotic therapy (dipyridamole, 150 mg, twice a day) in the male patients. Under therapy, in August 2000, patient 2 suffered a new cerebrovascular stroke, with neuro-ophthalmic signs (internuclear ophthalmoplegia) which completely resolved. Patients 1 and 2 maintain hemiparesia minor and patient 3 has important sequellae with right hemiparesia and disphasia. Patient 4 remains with no CVD, after 16 months.

Family history

Their non-consanguineous parents are healthy but an aunt and an uncle had LR and LV. Within these kindred with 6 sons and 3 daughters, 6 have LR, 3 of them with no cerebrovascular events (Table I).

Discussion

The association of LV and CVD occurring in 3 of our patients without any predisposing factor is the hallmark of Sneddon's Syndrome.

Sneddon described strokes, usually of limited extension, frequently with minor residual sequellae, that occur at a young age and may further repeat [1, 2]. Nevertheless in other reported cases of SS the CVD was haemorrhagic [28-31]. The 3 patients reported suffered the 1st cerebrovascular accident between the ages 23 and 42 years, and patients 2 and 3 had a 2nd cerebrovascular accident. CVD in patient 1 and 2 was thrombotic whereas patient 3 had intracerebral hemorrhages.

LR in SS begins also in youth, suffers progressive evolution, usually extending beyond the lower limbs and typically shows an open and irregular lattice pattern [1, 2]. It is the first symptom in the majority of patients, preceding CVD for many years, as occurred in these patients whose skin lesions preceded cerebrovascular events for 9 to 26 years [1,2]. The occurrence of livedoid vasculitis (LV) with seasonal ulcerations, as in our patients, was also described in four cases [16].

The histopathologic hallmark of LR in SS is an endothelitis and endarteritis obliterans [32, 33]. The single patient of these 4 who had alterations on skin histology showed partial endothelium detachment, which can be classified,

according to Zelger *et al.*, as the initial phase of this disease (Stage I) [33].

The complementary study was repeatedly normal or negative for pro-coagulant and pro-thrombotic risk factors, including the search for antiphospholipid antibodies (anticardiolipin, anti-beta2-GPI, both IgG and IgM).

Like in the first cases presented by Sneddon [1] and among the 153 cases later published as SS, women were affected in 71.24% (44 men, 109 women) [3, 5-31], but in this kindred only 3 males have developed SS, as in other reported cases [5, 10, 11, 14, 21, 28, 31].

In the first cases reported by Sneddon and Rebollo no studies for antiphospholipid antibodies were performed [1,2], but among the 153 patients published thereafter, seventy five – 49% (22 men, 53 women) – had positive anti-phospholipidic antibodies [5, 15-27], whereas seventy eight – 51% (22 men, 56 women) – presented negative antiphospholipid antibodies [3, 6-18, 20-24, 27-31]. Antiphospholipid Antibody Syndrome (APS) is an acquired multisystem disorder of hypercoagulation, occurring either secondary to LES and other autoimmune diseases or as a primary disease. Serologic markers are: lupus anticoagulant and anticardiolipin antibodies, usually associated with mild thrombocytopenia and abnormal partial thromboplastin time. Clinical features include: recurrent thrombotic events and repeated fetal loss. Cutaneous manifestations may occur and include LR, as in Sneddon's Syndrome. Nevertheless, noninflammatory vascular thrombosis is the most frequent histopathologic feature in APS [32], whereas in SS endothelitis and endarteritis obliterans are more characteristic [32, 33].

Although there are overlapping manifestations between SS and APS, namely LR and recurrent thrombotic events, their relationship remains controversial [15-27]. In our cases, repeatedly negative antiphospholipid antibodies as well as the absence of thrombocytopenia and abnormal partial thromboplastin time support the classification of SS as a rare but well-defined independent nosological entity, which is also in agreement with the opinions of Rehany and Zelger *et al.* [7, 8, 33].

There are other syndromes associating neurological and cutaneous alterations of vascular origin, where precocious cutaneous lesions may allow a correct diagnosis and the institution of early therapy, eventually preventing neurological sequelae [34]. Divry Van Bogaert's syndrome (DVB) is one of these rare entities that has to be distinguished from SS [34]. Described by a neurologist, in 1946, DVB is characterised by recurrent strokes in young patients preceded by LR localized mainly on the face and distal extremities. Skin biopsies show no vasculitis, but an increased number of dermal vessels with smooth muscles fibers disposed around them. CT scan and MRI can be identical to SS but cerebral angiography showing cortico-meningeal angiomatosis with collateral vascular anastomosis and narrow and helicine vessels in the midcerebral arteries, is diagnostic of DVB [34, 35]. Normal cerebral angiography in our patients does not support this diagnosis.

Most cases of Sneddon's Syndrome are sporadic, but there are also some rare familial cases reported [2-7]. In 1983 Rebollo *et al.* described three families, in 1986 Scott *et al.* reported a sister and a brother of another family, in 1994 Pettee *et al.* described SS in two brothers, in 1995 Lossos *et al.* reported another family and, in 1998, Rehany *et al.* described two siblings from one family. The inheritance

pattern was variable: autosomal dominant transmission for the families of Rebollo [2], Scott [3] and Lossos [6] and autosomal recessive transmission for the cases of Pettee [5] and Rehany [7]. The present report represents one of the largest number among siblings ever described and suggests a dominant autosomal transmission with incomplete penetrance and variable expressivity. ■

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