Livedo racemosa and cerebrovascular lesions (Sneddon syndrome): an experience-based review

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ABSTRACT

Introduction. Sneddon syndrome (SnS) is a rare entity characterized by livedo racemosa and cerebrovascular lesions. SnS is now regarded as common manifestation of different disease entities, including primary SnS, primary antiphospholipid syndrome–related SnS, and systemic lupus erythematosus–related SnS.

Development. The paper is divided into four parts. First, the differences between livedo reticularis and livedo racemosa are reviewed. Second, a historical analysis of the original descriptions of SnS is presented. Third, the results of the first prospective study of primary SnS, conducted by the author between 1977 and 1981 at Valdecilla Hospital, are set out. The series comprised eight patients (seven women and one man), representing 0.26% of the total number of cases of cerebrovascular disease admitted to the hospital during the five-year study period. Age at admission ranged from 18 to 59 years (mean, 46), whereas age of symptom onset varied between 10 and 33 years (mean, 19). The clinical, hereditary, neuroradiological and pathological features are reviewed. Finally, an updated review of the literature on SnS is presented, placing particular emphasis on nosological relationships of primary SnS with cerebral thromboangiitis obliterans and Divry–van Bogaert syndrome.

Conclusions. Primary SnS represents a new form of genetic, progressive, occlusive and non-inflammatory arteriopathy, which mainly involves medium-size vessels. Primary SnS, cerebral thromboangiitis obliterans, and Divry–van Bogaert syndrome should probably be considered as a single nosological entity.

KEYWORDS

Antiphospholipid syndrome; livedo racemosa; moyamoya syndrome; occlusive arteriopathy; Sneddon syndrome; stroke

Introduction

Sneddon syndrome (SnS) is a rare entity characterized by idiopathic livedo reticularis and cerebrovascular lesions.[1-4] The nosology of this syndrome is complex, especially considering that its semiology can be common to several neurological disorders. Moreover, even the definition of the characteristic cutaneous semiology of SnS, livedo reticularis, is not without controversy. SnS is now regarded as common manifestation of different disease entities, namely: *i)* idiopathic SnS with neither antiphospholipid (aPL) antibodies nor coexisting systemic lupus erythematosus (SLE); *ii)* primary antiphospholipid syndrome (APS)-related SnS; and *iii)* SLE-related SnS with or without aPL antibodies.[5-9]

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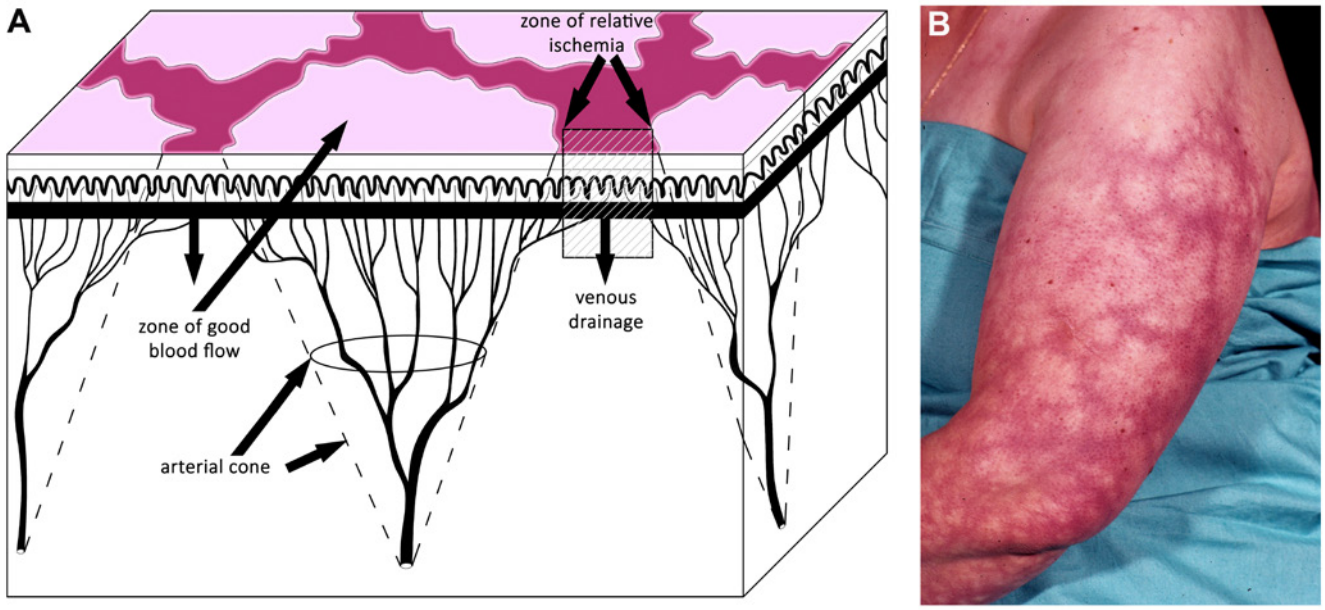

Figure 1. A) Schematic drawing of the vascular supply of the skin, with its arteriolar cones giving rise to a circular irrigation of good flow, which in any livedo manifests as whitish areas. At the margins of these circles are areas of relative ischemia, here drawn in a red violet color (adapted from Fleischer and Resnick[11]). B) Close-up view of the left arm, showing livedo racemosa (taken from case 2 from Rebollo et al.[4]).

The aim of this work is to review the nosology of SnS based on my experience with this syndrome, dividing the work into five sections: *i)* definition of livedo reticularis versus livedo racemosa; *ii)* concerns about the original description of the SnS; *iii)* contributions of our group to the knowledge of SnS; *iv)* epilogue: updated SnS clinical data; and *v)* conclusions.

Development

Livedo reticularis versus livedo racemosa

The word livedo was introduced to describe a violet discoloration of the skin due to local circulatory disturbance, as opposed to cyanosis of central origin.[10] To explain the livedo pattern in physiological terms, it has been postulated that the cutaneous vasculature consists of a series of one- to three-centimeter cones, with the apex of each cone located deep in the dermis at the site of ascending arteriole (Figure 1A).[11] According to this cutaneous vascular microanatomy, any physiological or pathological process that impedes blood flow to and through the skin could produce an increased proportion of deoxygenated hemoglobin, thereby resulting in prominent livid coloration in the predominantly venous areas at the margins of the cones.

The term livedo reticularis is often used interchangeably with livedo racemosa; however, the differentiation between both forms of livedo is clinically relevant.[12] It is worth noting that there is a debate in the literature about the nomenclature of racemosa (usually used in European papers) versus reticularis (usually used in US papers). The term livedo racemosa was first introduced in 1907 by Ehrmann,[13] as follows: "tendril-like bluish pattern reminiscent of forking lightening, which intensified in the cold as a sign of passive hyperemia, somewhat cooler than the surrounding skin" (Supplementary material, figure S1).[13] Livedo racemosa is characterized by a violaceous netlike patterning of the skin similar to the familiar livedo reticularis, from which it differs in terms of location (more generalized and widespread; Figure 2)[4] and form (irregular, broken, circular segments) (Figure 1B),[4] appearing both on the limbs (particularly the lower

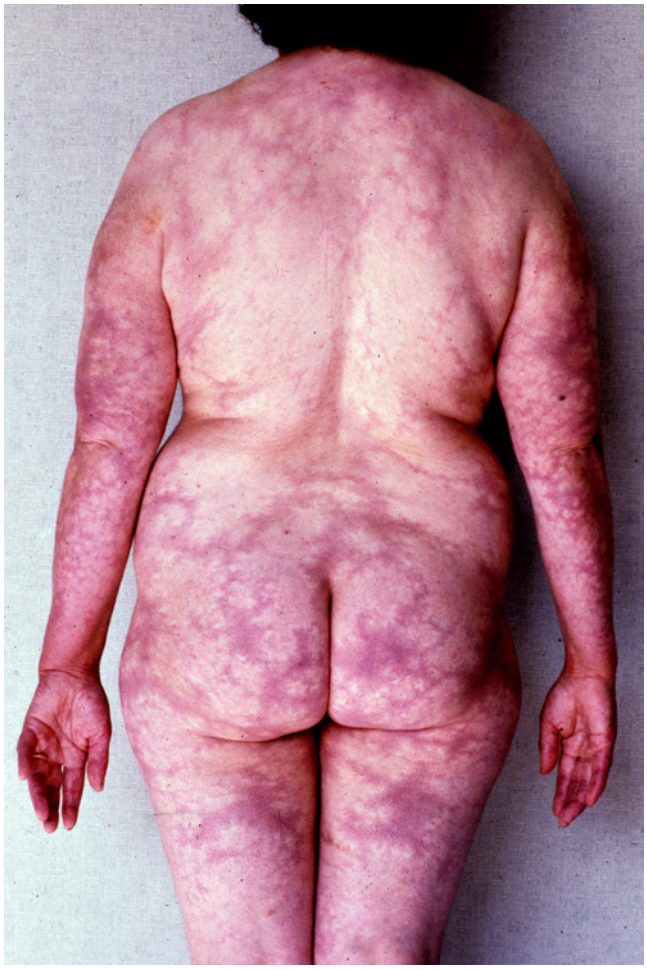

Figure 2. Livedo racemosa generalisata (taken from case 2 from Rebollo et al.[4]).

limbs) and also on the trunk and/or buttocks, and skin biopsy results (normal in livedo reticularis and positive in livedo racemosa).[8,12,14-18] Skin discoloration in livedo racemosa remains unchanged to warming, in contrast to livedo reticularis. Livedo racemosa is almost always associated with a pathological condition; conversely, livedo reticularis is usually caused by functional factors such as vasoconstriction in the cold (cutis marmorata). The spectrum of differential diagnosis for both forms of livedo is summarized in Table 1.[12]

In their seminal paper on SnS with or without aPL antibodies, Francès et al.[5] established a novel system for evaluating livedo. When irregular broken circles were present, the livedo was considered to be racemosa. On the other hand, when the regularity of the fishnet reticular pattern led to unbroken circles, it was considered to be regular livedo. The thickness of the fishnet reticular pattern was also taken into account. Livedo was considered large or fine according to the width of the branching pattern, that is, wider or equal to versus finer than 10 mm, respectively. Thus, four types of livedo could theoretically be observed: fine livedo racemosa, large livedo racemosa, fine regular livedo reticularis, and large regular livedo reticularis (See Figures 1B and 2, and figures in the Genetic data section).[4]

Concerns about the original description of the Sneddon syndrome

In 1979, the term Sneddon's syndrome (*Cerebrovascular lesions and livedo reticularis*) was introduced into the neurological literature by Rumpl and Rumpl.[2] Indeed, in 1965, Sneddon had described the cases of six patients (five women and one man) who had in common a series of cerebrovascular incidents, which were of limited and benign nature, often leaving little disability.[1] The age of symptom onset was between 20 and 42 years, though many of them had livedo before this age. Benign hypertension was present in some but not all patients, with no significant kidney alterations as shown by normal renal function tests. It should be noted that the livedo was obvious and widespread, always affecting the limbs and frequently also the trunk. Further study failed to show any evidence of polyarteritis nodosa, SLE, or thrombocythemia, with the authors suggesting an arteritis of unrecognized type as the possible etiology. Very opportunely, Sneddon pointed out that "the only comparable description is that of Champion and Rook[19] who demonstrated a somewhat similar patient at the Royal Society of Medicine [RSM] in 1960." Let us turn our attention, then, to the contribution of Champion and Rook.

On 17 March, 1960, in a written communication at the RSM, Champion and Rook described the case of a man, aged 39 years, who showed a clinical picture characterized by hypertension, angina pectoris, and two small cerebral thromboses.[19] Progressive discoloration of the skin started in 1954, and consisted of widespread, but rather patchy, livedo reticularis that was most intense on the buttocks, arms, and legs (see their figure 1). Routine laboratory findings were normal. Skin biopsy showed a small artery, deep the in corium, exhibiting endarteritis obliterans, with the internal elastic lamina being intact; wisely, the authors indicated that this appearance

was not in any way characteristic of polyarteritis nodosa. Muscle biopsy revealed no abnormality. They concluded that the nature of the arterial disease was therefore uncertain. Sneddon himself participated in the discussion of this work, noting that he had seen three similar cases and that to his knowledge the skin changes were suggestive of generalized vascular disease, but that this may not be polyarteritis nodosa.

Two years later, Church[20] presented another written communication at the RSM entitled "Reticular livedo with cerebrovascular lesions". His conclusion was as follows: "I do not think that this is polyarteritis nodosa but do think that an arteritis of unknown etiology must be responsible and the syndrome is worth bearing in mind when confronted with reticular livedo."

Therefore, in the early history of SnS, at least five great names stand out (Figure 3): Ehrmann, for differentiating livedo racemosa from functional livedo reticularis; and Champion, Rook, Church, and Sneddon, for proposing that the arteriopathy underlying the syndrome is novel, but of unknown cause.[1,13,19,20] I would like to end this section with a statement by Sneddon himself[1]: "I feel that a greater awareness of the syndrome may lead to recognition of more cases and the discovery of the etiology which will, I think, be a type of endarteritis obliterans, perhaps similar to Takayasu's arteriopathy".

Table 1. The spectrum of differential diagnosis in neurological patients with livedo reticularis and livedo racemosa.

Livedo reticularis
Cutis marmorata
Amantadine-induced livedo reticularis
Livedo racemosa
Sneddon syndrome
Divry–van Bogaert syndrome
Tromboangiitis obliterans
Antiphospholipid syndrome
Systemic lupus erythematosus
Polyarteritis nodosa
Herman syndrome
Migraine
Cholesterol embolization syndrome
Livedoid vasculopathy
Thrombocythemia
Polycythemia vera
Pernicious anemia
Disseminated intravascular coagulation
Cryofibrinogenemia
Pancreatitis
Graves' hyperthyroidism associated with anticardiolipin antibodies
Rheumatoid arthritis
Sjögren syndrome
Dermatomyositis
Scleroderma
Arteritis temporalis
Calciphylaxis in chronic dialysis patients
Hyperoxaluria
Embolism from arterial or cardiac myxoma
Infectious diseases (eg, post-streptococcal syndromes)

Adapted from Kraemer et al.[12]

Contributions of our group to the understanding of Sneddon syndrome

1. My first evaluation of a patient suffering from livedo racemosa and stroke

In 1971, as a resident in neurology at the Clínica Puerta de Hierro (Madrid), I attended a 40-year-old woman who had been referred to our outpatient clinic due to recurrent transient ischemic attacks.[21] The patient reported many episodes of alternating hemiparesis and monocular amaurosis fugax, followed by a rapid and complete recovery. Such episodes had occurred several times per year during the previous decade. She reported no headache or constitutional symptoms; blood pressure, monitored by her general practitioner, had always remained normal. During her physical examination, the only finding was livedo racemosa generalisata, whose presence the patient reported since adolescence. We were very surprised, as neither previous neurological articles nor textbooks of neurology had mentioned livedo racemosa generalisata at that time. After a search of *Index Medicus*, I found the paper by Sneddon,[1] who was apparently the first to report the association between livedo reticularis and stroke (see above). In line with the recommendation of Sneddon himself, we considered polyarteritis nodosa, SLE, Takayasu arteritis, and thrombocytopenia as possible etiological causes. Analytical studies and skin and muscle biopsy did not support any of these possibilities. After lively debate, a diagnosis of suspected polyarteritis nodosa was established, and treatment was started with prednisone for several months with subsequent tapering. To my knowledge, it was easier to rule out the causes for the exceptional syndrome combining livedo racemosa generalisata and stroke. The long and benign clinical course (around 30 years for livedo racemosa), as well as the absence of constitutional symptoms, seemed to constitute strong arguments against any systemic vasculitis.

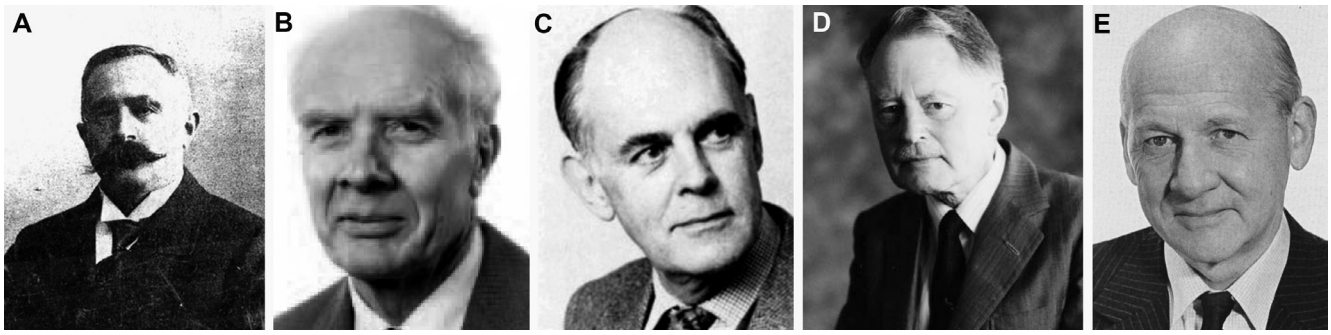

Figure 3. Photographs of pioneers in the description of livedo racemosa and Sneddon's syndrome. A) Salomon Ehrmann (1854-1926), the Austrian dermatologist who identified livedo racemosa (see Supplementary material; figure S1). B-E) Four British dermatologists who described the syndrome of cerebrovascular lesions and livedo reticularis: B) Robert Harold Champion (1929-2004); C) Arthur James Rook (1918-1991); D) Ronald Edward Church (1923-2007); and E) Ian Bruce Sneddon (1915-1987). See text for details. The photographs were downloaded from the Internet and are in the public domain.

By then, Sneddon's own reflection was on my mind[1]: the syndrome could be a type of endarteritis obliterans of a previously unknown type.

2. Our prospective study in Sneddon syndrome at Valdecilla Hospital (1977-1981)

Background and methods. Already installed at Valdecilla Hospital in 1974 (for more historical details, see Berciano[21]), I proposed in 1976 that Dr Mariano Rebollo write his doctoral thesis, under my tutelage, on the redefinition of the nosology of SnS; it should be noted that at that the time there were still no articles on the syndrome in the neurological literature. We planned to include patients showing livedo racemosa and cerebrovascular lesions of any type (ideally two or more) who would be seen in the five-year period 1977-1981, to whom the following study protocol would be applied (for details, see Rebollo et al.[4]):

— Detailed medical history, including cardiological assessment in cases of suspected heart disease.

— Electrocardiography, electroencephalography, chest radiography, hand and cerebral angiography, brain CT scan, and skin and digital artery biopsies.

— Routine blood, urine, and cerebrospinal fluid analysis, and syphilis serology.

— Immunological profile including antinuclear antibodies, lupus erythematosus cell preparation, rheumatoid factor, cryoglobulins, hepatitis-associated antigen, protein immune-electrophoresis, CH50 procedure, C3, and circulating immune complexes. It is worth noting that aPL antibodies had not yet been described at the time.

— Coagulation profile.

Results: sex, age and initial symptoms. Over the five years of the study, we collected 8 SnS patients (7 women and 1 man; numbered cases 1 to 8), whose ages ranged from 18 (case 1) to 59 years (case 7) (mean, 46).[3,4] Age at onset ranged between 10 (case 8) and 33 years (case 3) (mean, 19). None of the 8 patients were smokers. Initial symptoms were livedo racemosa in seven cases and stroke in one.

Epidemiology. During the five-year study period, a diagnosis of cerebrovascular disease (WHO/ICD-8 codes 430-438) was made in 3006 patients; therefore, in this series, SnS represented 0.26% of the total cases of cerebrovascular disease.[3,4]

Cutaneous signs. Extensive livedo racemosa was a constant, progressive sign involving all four limbs and the trunk (Figures 1B and 2).[3,4] Livedo worsened in cold weather and during the acute phase of the neurological deficits. Ulcerations and cutaneous nodules were not observed in any case. With the exception of case 5,

livedo racemosa preceded the neurological symptoms by several years.

Peripheral ischemic manifestations. All patients had early, but not severe, signs of chronic ischemia in the extremities.[3,4] These were acro-erythrocyanosis, cold hands and feet, impaired or absent pulsation in the posterior tibial and dorsalis pedis arteries, and typical Raynaud phenomenon (cases 1, 4, 6-8).

Arterial hypertension. Six patients had mild hypertension, which was easily controlled with temporary diuretics and a sodium-restricted diet.[3,4]

Neurological manifestations. These consisted of ischemic strokes (cases 1-5 and 8), transient ischemic attacks (TIA; case 6), epileptic seizures (cases 2 and 7), and progressive dementia (case 2-5).[3,4] Each patient presented a minimum of two strokes, with the first occurring before the age of 45 years. The strokes were of limited extent, leaving little residual deficit. The predominant signs and symptoms were hemiparesis, central facial palsy, aphasia, and hemianopia, and less frequently hemihypesthesia, paresthesia, and pseudobulbar dysarthria. Mental deterioration manifested after the first stroke in all cases, and was severe in cases 2 and 4.

Laboratory investigations. The results of laboratory studies, including immunological and coagulation profiles, were normal or irrelevant.[3,4] Even in the absence of aPL antibodies, these eight cases could be classified as idiopathic SnS.

Hand angiography. Findings were abnormal in all cases.[3,4] The changes observed on the angiogram were segmental narrowing and dilatation in the common and proper digital arteries, together with multiple narrowing obstructions and marked reduction of caliber in the latter (Figure 4).[4]

Cerebral angiography. This was also abnormal in all cases.[3,4] The changes can be divided into three groups: *i)* obstruction and stenosis located in distal (Figure 5)[4] or basal branches of intracranial arteries; *ii)* collateral circulation in the brain, which included transdural anastomoses, anastomoses between intracranial arteries, and "moyamoya" type anastomosis via deep perforating vessels at the base of the brain; and *iii)* intracranial arteriovenous malformation (AVM) in one patient (see below).

Brain CT scan. As illustrated in Figure 6,[4] focal areas of low density were seen in all patients except case 6; two or more hypodense areas were observed in cases 2-5.[3,4]

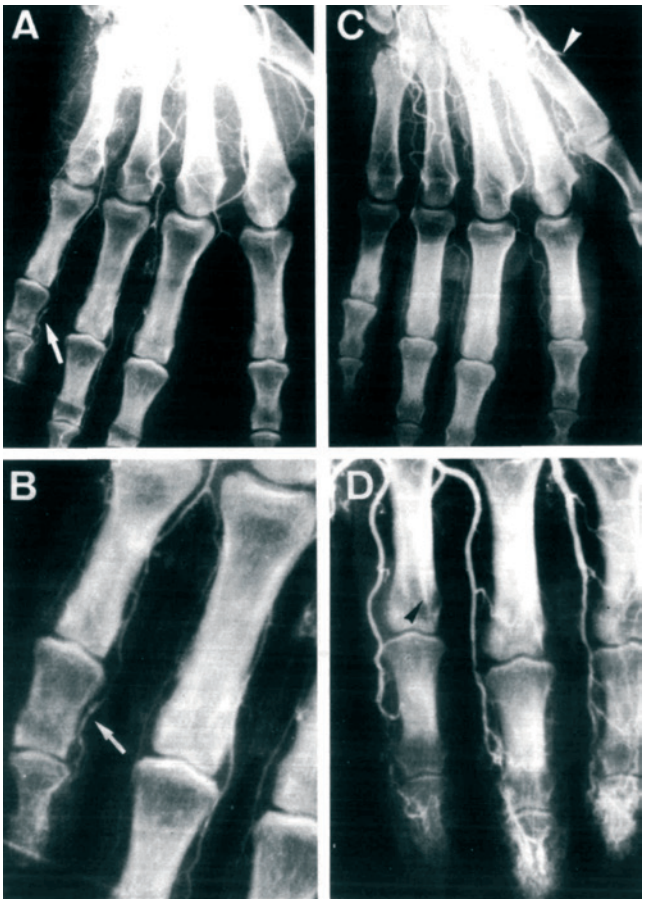

Figure 4. Hand arteriograms illustrating widespread narrowing and irregularity (arrows) of the lumen of the digital arteries, with several displaying apparently total obstruction (arrowheads). A and B, case 2; C, case 6; and D, case 4 in the series by Rebollo et al.[4]

A constant finding was a variable degree of cortical atrophy with ventricular dilatation. Post-contrast studies carried out in cases 1, 2, and 6-8 did not provide further information. MRI was not yet available at our institution.

Skin biopsy findings. Skin biopsy results were normal in all cases.[3,4] In retrospect, this negative feature is probably the result of not having selected an appropriate biopsy site (skin is not affected in the center of the livedo racemosa circles), inadequate size of the biopsy (1 to 2 cm), and/or depth of the biopsy not reaching the dermis-subcutis boundary.[7,22,23] Moreover, skin biopsy had a sensitivity of

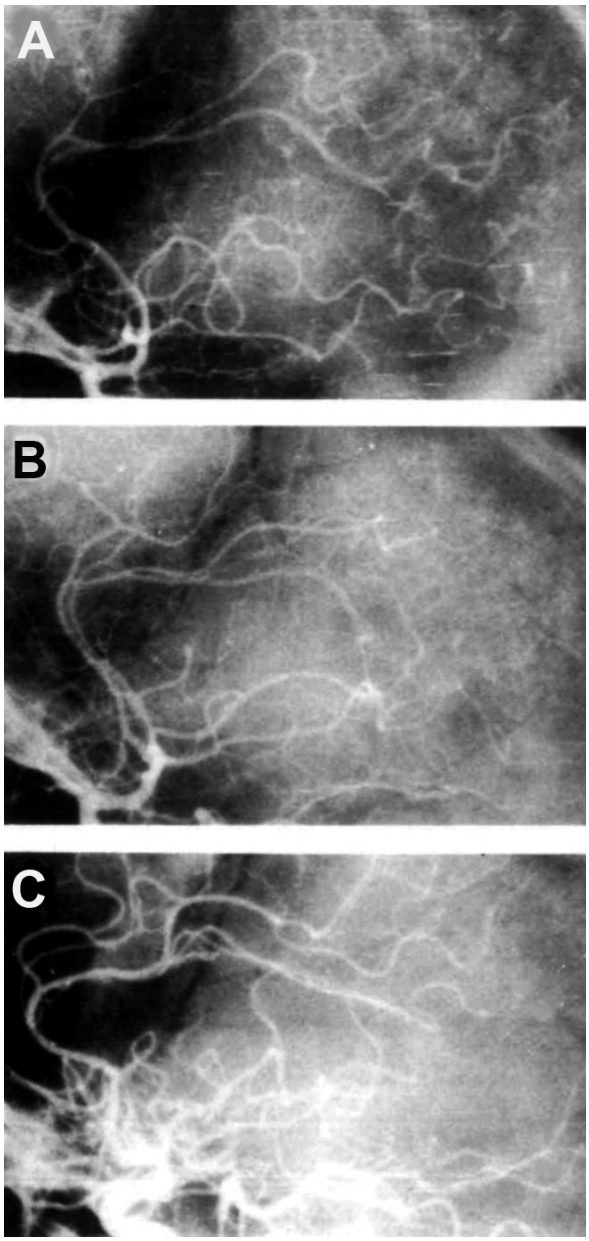

Figure 5. A-C) Carotid angiograms showing narrowing and occlusions in the distal segments of opercular branches of middle cerebral artery, and distal pericallosal artery. A and B, case 2; C, case 3. Taken from Rebollo et al.[4]

27% with one biopsy, as performed in our series, 53% with two biopsies, and 80% with three biopsies taken from white areas.[24]

Digital artery biopsies. Our findings are illustrated in Figure 7.[3,4] Alterations were observed in all 7 patients undergoing digital artery biopsy. There was focal, segmental, intimal hyperplasia. The intimal tissue consisted mainly of fibro-elastic proliferation with small numbers of intimal smooth muscle cells. The internal elastic lamina, except in isolated zones of focal absence or reduplication, appeared well preserved. The tunica media of these arteries was normal, but tunica adventitia showed slight fibrosis. In case 4, the artery was completely occluded by an old thrombus, which was organized and re-canalized. We found no evidence of either acute or chronic inflammation, fibrinoid necrosis, or lipid deposits, and immunofluorescence studies were negative in all cases (see Rebollo et al.[4] for further details).

Genetic data. As noted above, when we began our study, SnS was catalogued as an arteriopathy of unknown origin, whose histopathological basis was an endarteritis obliterans similar to that described in Takayasu arteritis,[1] that is, it was categorized as a sporadic syndrome, a notion that we overturned in our study.[3,4] Let us analyze the issue in greater detail.

In 1978, in one of case 2's follow-up consultations (see Figures 1B and 2),[4] she came accompanied by her 42-year-old sister, who had never been ill. It was a hot day, so she asked permission to take off her jacket. To my surprise, on her upper arms and to a lesser degree on her forearms there was a florid livedo racemosa (Figure 8A). With the reasonable suspicion that SnS may be a familial disorder, we then requested permission to conduct a physical examination of the extended family of case 2 (figure 9A).[4] We examined 28 members of this family in three generations and found that 13 of them had livedo racemosa (Figure 8B). Two siblings of the proposita (cases II-2 and II-3) and one of her nieces (case III-13) also had acro-erythrocyanosis, erythema pernio, and Raynaud phenomenon. Hand angiography in case II-2 showed similar findings to those of the older sister, the proband patient (see Figure 4A, B).[4] CT scans of cases II-3, III-11, and III-13 were normal.

Subsequently, we decided to take a detailed family medical history by asking the index cases about history of livedo racemosa or stroke in their relatives. In case 1 (Figure 9B),[4] a great aunt of the patient, aged 51 years, had had diffuse livedo reticularis since she was young, in addition to hypertension, strokes, and dementia in the last few years. However, examination of the parents and siblings of the proposita revealed no abnormalities. In case 7 (Figure 9C),[4] according to the information from the proband, the father and one of the patient's six siblings

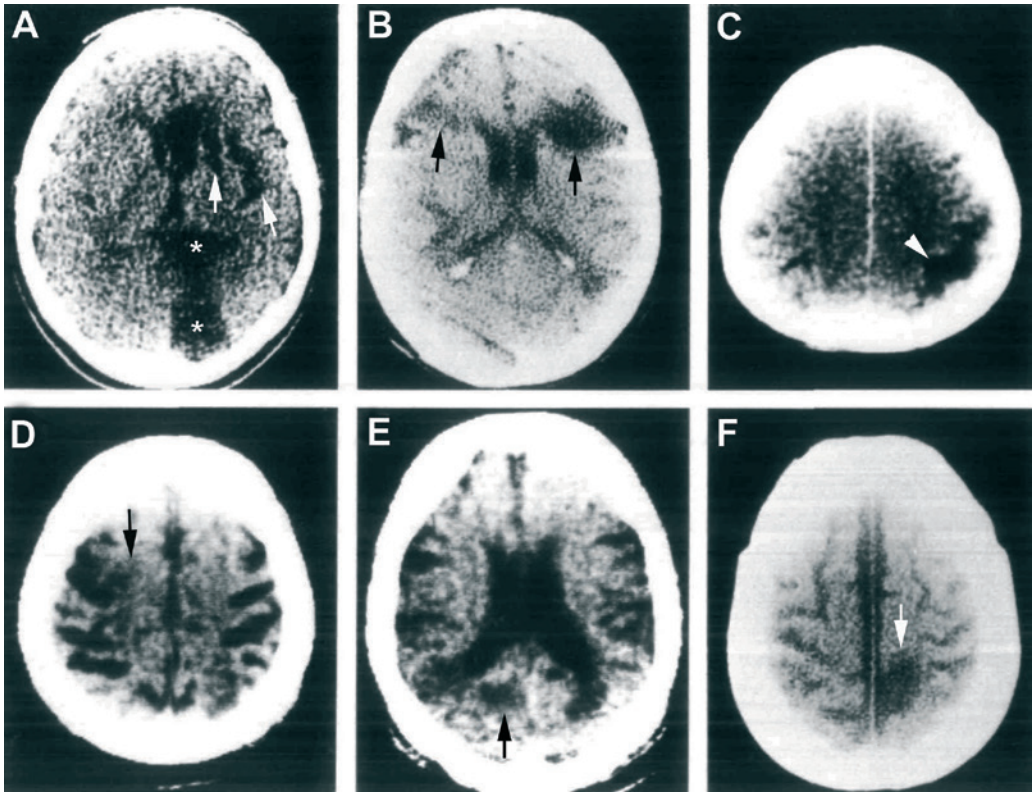

Figure 6. Brain CT scans showing multifocal, multi-territorial, and cortical-subcortical infarcts of small- to medium-size arteries (arrows), and one extensive infarct in the territory of the left posterior cerebral artery (asterisks). Note diffuse cerebral atrophy (D-F) and focal brain atrophy (C; arrowhead). A, case 3; B, case 5; C, case 7; D-E, case 2; and F, case 4. Taken from Rebollo et al.,[4] with modifications.

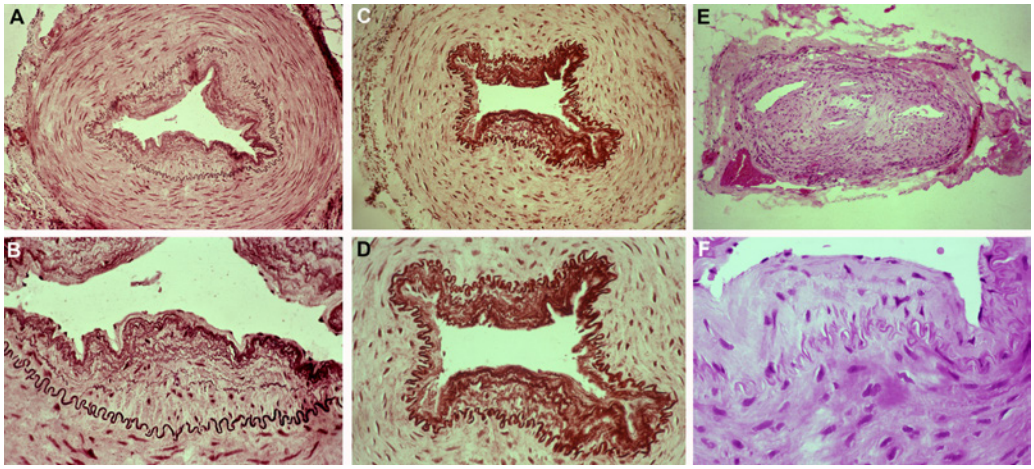

Figure 7. Histopathological features in the digital arteries. A, C) Complete transverse sections showing preservation of the normal arterial structure with just intimal hyperplasia with elastosis (orcein, 100× before reduction). B, D) At higher magnification, note the variable degree of intimal laminated elastosis (orcein, 200× before reduction). E) Complete section of a digital artery with a re-canalized thrombus (hematoxylin and eosin, 100× before reduction). F) Detail of intimal hyperplasia showing proliferation of endothelial and myoepithelial cells, but no inflammatory cells (hematoxylin and eosin, 400× before reduction). A, B, and F, case 6; C and D, case, 2; and E, case 4. Taken from Rebollo et al.,[4] with modifications.

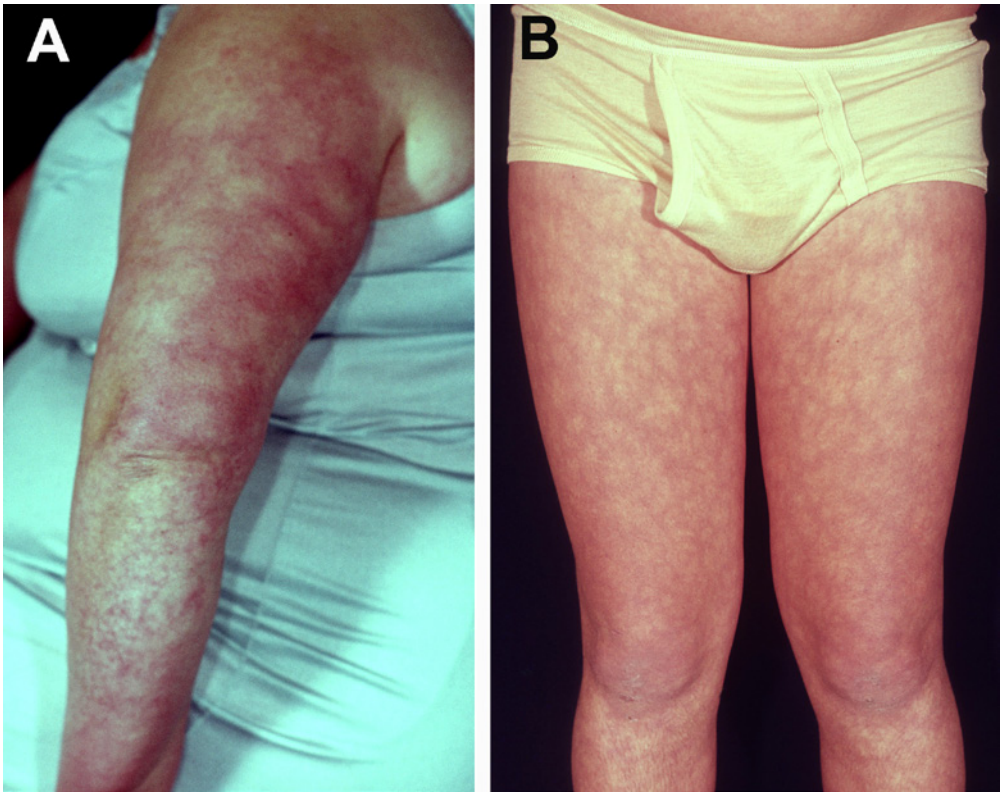

Figure 8. A) Close up photograph of the left upper arm and forearm showing livedo racemosa in the sister of case 2 (case II-2 in Figure 9A). B) Close-up photograph of the thighs in an asymptomatic boy aged 11 years (case III-11 in figure 9A), showing large livedo reticularis (see text for explanation).

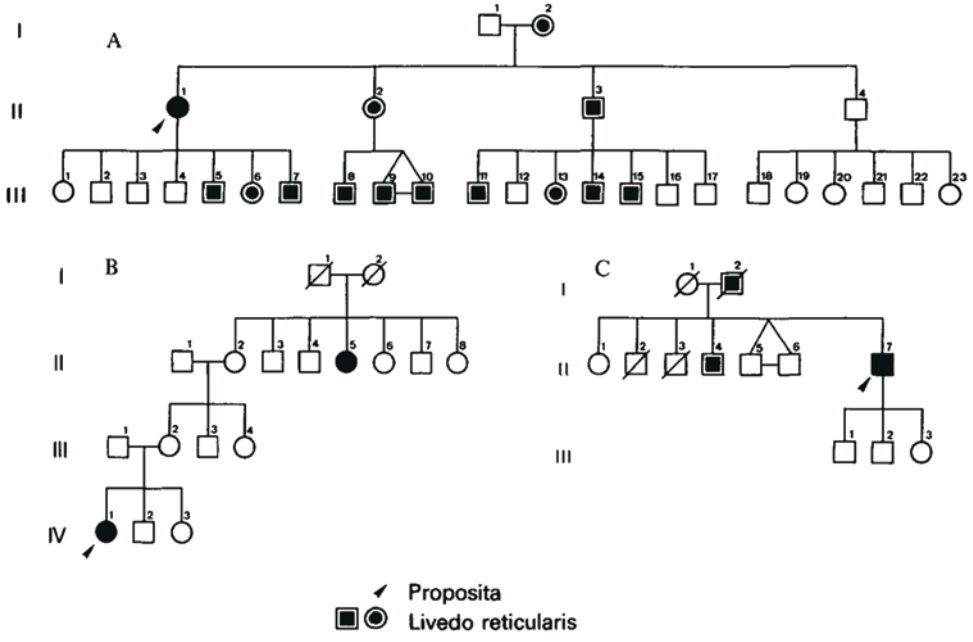

Figure 9. Pedigrees of cases 2 (A), 1 (B), and 7 (C). Taken from Rebollo et al.[4]

had generalized livedo reticularis. In the remaining five index cases, family history was negative.

We argued that in three of our cases (cases 1, 2, and 7), the disease, either in its clinical entirety or with livedo racemosa as the only clinical manifestation, was inherited. In the family of case 1 (Figure 7A),[4] the disease is apparently transmitted with autosomal dominant inheritance with incomplete penetrance; whereas family pedigrees of cases 7 and 2 (Figure 7B, C)[4] correspond fully to what is to be expected in simple autosomal dominant transmission. This question was neglected in a subsequent review of the Mendelian etiologies of stroke,[25] which led me to write a reply,[26] after which SnS was included in the Online Catalog of Human Genes and Genetic Disorders (OMIM # 182410).

Differential diagnosis. This section includes a wide group of syndromes, which are updated in Table 1.[12] Rebollo et al.[4] analyzed in detail two other entities that combine livedo racemosa and brain lesions: cerebral thromboangiitis obliterans (CTAO) and Divry–van Bogaert syndrome, which in the literature are considered distinct entities from SnS. After a literature review, we found that the clinical, arteriographic and autopsy studies in CTAO are similar to those described for SnS, without the inflammatory vascular histopathologic lesions characteristic of Buerger disease. For this reason, we proposed that CTAO and SnS are one and the same entity.[3,4,27] The question of Divry–van Bogaert syndrome is addressed in the following section.

Case 4: a severe, fatal form of Sneddon syndrome with radiological moyamoya pattern and autopsy study. This right-handed patient was admitted in 1980, aged 53 years, with four-year history of progressive cognitive decline.[3,4] At ages 39 and 52 years she had experienced two sudden, reversible episodes of right hemiparesis. She had presented generalized livedo racemosa since childhood (Figure 10A).[28] She had had seven pregnancies, all of which had ended in spontaneous abortion. Vital signs were normal, with blood pressure of 140/80 mm Hg. There was grade II pansystolic murmur at the cardiac apex. Neurological examination showed disinhibition, moderate fluent dysphasia, oppositional paratonic rigidity, dysarthria, shuffling gait, and generalized hyperreflexia, with both plantar responses being extensor. Repeated laboratory studies including immunological and coagulation profiles (see above) were normal or negative. Electroencephalography and electrocardiography findings were normal; echocardiography was not performed. Figure 10B and C[28] illustrate the results of cranial angiographic findings, essentially consisting of moyamoya pattern and an AVM in the right occipital lobe. A CT scan showed widespread cortical-subcortical atrophy and multiple brain infarcts (see Figure 6F[4]; unfortunately, this is the only image available).

Two years later, she was readmitted with an acute, afebrile picture of distal ischemia in the upper and lower limbs that caused dry gangrene, and died 8 days later. Pathological study results were not yet available when we had finished writing our first two papers on SnS.[3,4] For purely circumstantial reasons, the results of the necropsy study could not be reported until 2018.[28] Brain and general autopsy findings are illustrated in Figure 10D-O.[28] For the current investigation, we reviewed archived photographic and pathological materials. The brain weighed 855 g. Figure 10D-F[28] shows macroscopic brain findings. Microscopic study revealed widespread non-inflammatory occlusion of large- to medium-sized arteries, and arterioles (Figure 10G-I).[28] We found no evidence of either acute or chronic inflammation, fibrinoid necrosis, or lipid deposits. Figure 10J[28] illustrates marked hyperplasia of leptomeningeal vessels. Figure 10K[28] shows the histological appearance of the observed occipital AVM. There were numerous sub-cortical and intra-cortical infarcts (Figure 10L).[28]

General autopsy showed non-bacterial thrombotic endocarditis (Libman-Sacks) of the mitral and aortic valves (Figure 10M),[28] as well as systemic arteriopathy involving all large- to medium-sized vessels examined, with occasional presence of mural thrombi (Figure 10N, O).[28]

As mentioned earlier, this patient was included within our series of idiopathic SnS,[3,4] though the possibility of APS-related SnS cannot entirely be excluded, given that, inevitably, blood tests for aPL antibodies were not yet available at the time of admission. Nevertheless, the possibility of SLE was ruled out, and the patient's normal coagulation profile, including activated partial thromboplastin time and platelet function study, argues in favor of idiopathic SnS.[5,7]

Our autopsy study confirmed that the pathological basis of SnS is a systemic, occlusive, non-inflammatory vasculopathy mainly involving large- to medium-sized arteries and arterioles. It was characterized by intimal hyperplasia with muscular-elastic proliferation, which could, in turn, lead to re-canalized thrombosis.[4,29,30]

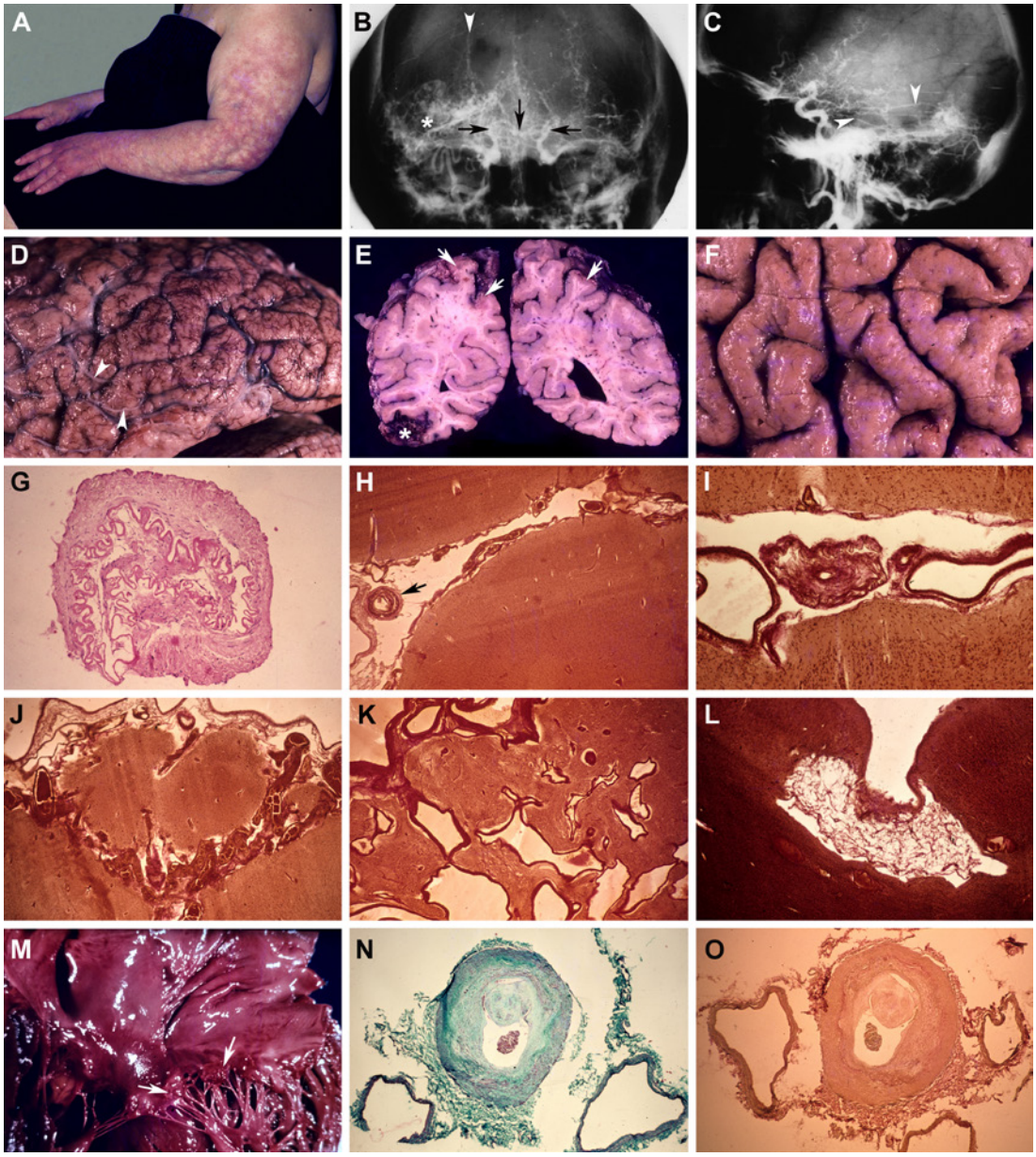

Figure 10. A) Livedo racemosa of the left upper limb. Simultaneous left carotid and right retrograde brachial angiography (B) and right retrograde brachial angiography (C) showing complete occlusion of both anterior and middle cerebral arteries (arrows) and an arteriovenous malformation (AVM) in the right occipital lobe (asterisk) supplied by the tentorial branch of the carotid artery and meningeal branches of the occipital and middle meningeal arteries (arrowheads); a collateral network of vessels is visible in the base of the brain, as reported in moyamoya syndrome. D) Left brain convexity, displaying a profuse network of subarachnoid collateral vessels; note the presence bloodless white vessels corresponding to occluded arterioles (arrowheads). E) Posterior surface of coronal section through the posterior horns of the lateral ventricles, showing dilated atrium of the lateral ventricles, prominent vascular profiles in subcortical white matter, several intra-cortical infarcts (arrows), an AVM of the right occipital lobe (asterisk), and brain atrophy. F) After dissecting down the meninges, this close-up picture shows extensive granular atrophy. G) Transverse section of the middle cerebral artery, showing that its lumen is occupied by a partially re-canalized thrombus; note also intimal hyperplasia, preservation of the internal elastic layer, and the absence of inflammatory infiltrates (hematoxylin and eosin, 63× before reduction). H) Low-power view of a cerebral sulcus showing an arteriole with hypertrophied internal elastic layer (arrow) and hyperplasia of intra-sulcal vessels (orcein, 25× before reduction). I) At higher magnification, note the presence of a sulcal arteriole with intimal hypertrophy and reduplication of the internal elastic lamina, reducing its lumen, which is flanked by two larger venules (orcein, 100× before reduction). J) In some areas, hyperplasia of subarachnoid vessels is so intense that it acquires the appearance of meningeal angiomatosis (orcein, 40× before reduction). K) Characteristic texture of the right occipital AVM, consisting of vascular clusters without any intermediate capillary network, and with brain parenchyma interposed (orcein, 63× before reduction). L) Small intra-cortical infarct (orcein, 40× before reduction); similar lesions (not shown) were observed in subcortical areas. M) Note the presence of vegetations in the mitral valve (arrows). N, O) These transverse sections of a brachial artery show widespread degeneration and enlargement of the intima, with the internal elastic lamina being displaced outward and focally reduplicated. There is a voluminous thrombus adhered to the arterial wall. Again, note the absence of inflammatory infiltrates (Masson trichrome and orcein, 40× before reduction). Taken from Berciano and Terán-Villagrá.[28]

The observed marantic endocarditis (Libman-Sacks), which did not cause multi-territorial brain infarcts and for a long time remained subclinical until the final episode of systemic embolism, supports the notion that idiopathic SnS is frequently associated with heart valve lesions.[31] Furthermore, such systemic occlusive arteriopathy concurs with the proposal that valvular heart disease does not influence the type of brain infarct, namely that ischemic strokes are caused by widespread cerebral arteriopathy.[31]

Cerebral angiography showed occlusion of anterior and middle cerebral arteries, with collateral anastomosis via perforating vessels at the base of the brain, showing a moyamoya pattern. In 1999, Carhuapoma et al.[32] reported eight cases of moyamoya syndrome with SnS, including the one described here; another two similar cases were subsequently reported.[33,34] Four cases were associated with the presence of lupus anticoagulant or anticardiolipin antibodies. These authors emphasized that when the few cases of moyamoya syndrome that were pathologically examined were reviewed, a striking resemblance with pathological findings in SnS was observed[35]; specifically, there was a remarkable absence of vascular inflammatory changes in both conditions, as well as prominent hyperplasia and fibrosis associated with intimal thickening (see Figures 7 and 10).[4,28] According to Yamashita et al.,[35] the changes in the lenticulostriate arterioles may be divided into two types: dilated vessels with relatively thin walls, and thick-walled arterioles showing luminal stenosis. Therefore, this might facilitate the presence of dissecting or saccular aneurysms probably caused by severe hemodynamic stress of moyamoya vessels, which ultimately leads to vessel wall disruption and intracranial hemorrhage that might be intraventricular,[36-38] intracerebral,[39-43] or microbleeds associated with small vessel ischemia.[44] To the best of my knowledge, the cerebral AVM observed has not been reported in SnS.

Macroscopically, the brain shows a profuse network of vessels, some of which are occluded arterioles, and multifocal infarcts (see Figure 10D, E).[28] I interpret that this vascular network is due to profuse collateral circulation via transdural anastomoses and anastomoses between intracranial arteries,[3,28] which are certainly very similar to the autopsy features of Divry–van Bogaert syndrome.[45-47] Given that in both syndromes we are confronted with angiomatosis secondary to systemic occlusive arteriopathy, it is reasonable to propose that familial idiopathic SnS and Divry–van Bogart syndrome are the same nosological entity.[28,48] Should my pathogenic proposal be accepted, as already indicated by Rebollo et al.,[4] I would suggest that the two OMIM reference numbers (#206570 for Divry–van Bogaert syndrome and #182410 for Sneddon syndrome) be merged.

Treatment. Empirically, our patients were treated with antiplatelet drugs (aspirin 250 mg and dipyridamole 300 mg daily).[3,4] With the exception of case 4 (see above), the remaining seven patients remained stable in the following years.

Summary of our contributions. Our study of eight presumptive cases of primary SnS demonstrated that the syndrome is a well-defined occlusive arteriopathy, which is often genetically determined.

Epilogue: a brief nosological update

In the last four decades, great advances have been made in SnS nosology, which are briefly reviewed below. I shall begin with APS, whose original description[49] coincided in time with the publication of our first papers on SnS.[3,4]

1. Antiphospholipid syndrome

Originally reported by Hughes in 1983,[49] APS is a systemic autoimmune disorder in which different prothrombotic factors interact to induce arterial and venous thrombosis.[50-52] It is defined by a combination of at least one clinical feature characterized by vascular thrombosis (venous, arterial, or both) or pregnancy morbidity and elevated titers of aPL antibodies, namely, lupus anticoagulant, anticardiolipin antibodies, and/or anti-β2 glycoprotein antibodies. The triple-positive profile for these antibodies appears to be the most important factor in thrombosis, with a relative risk of 33.[52] Other prothrombotic factors are included under thrombophilia work-up (protein C, protein S, factor V Leiden, prothrombin G220210A, and methylenetetrahydrofolate reductase mutations).[5] APS can be primary, if it occurs in the absence of any underlying disease, or secondary, if it is associated with another autoimmune disorder, usually SLE. In the seminal observational study of 1000 patients with APS from 13 European countries, patients were predominantly female (82%), with a mean age at study entry of 42 years; focusing on manifestations related to SnS, livedo reticularis was detected in 24% of cases, while stroke occurred in 20%.[50] The incidence of SnS in primary APS cases with triple-antibody positivity has been established at 8%. From here on, SnS is

basically categorized into a primary form, when it is not associated with aPL antibodies, and a secondary form, when this association does exist.[5] In any case, fewer than half of patients with SnS present aPL antibodies.[8]

2. Other updated clinical data

In this section I have relied on original papers[5,23,30,31,53-61] and review papers.[6-9,62] Starting from SnS series reported after ours, it has been established that the disease passes through three basic stages.[62] Stage I is the prodromal phase, which is characterized by migraine-like headaches and dizziness; these may even precede livedo racemosa, which in most cases is the first manifestation of the disease. Stage II is the almost fully developed classic semiology, with most patients displaying multifocal symptoms including TIAs and/or ischemic strokes. Finally, stage III is characterized by progressive cognitive decline.

The clinical data from our primary SnS series, presented here, are largely consistent with what has subsequently been described in the literature. Therefore, I will focus on certain issues, whether corroborative or novel, as follows.

Epidemiological studies have confirmed that SnS is a rare syndrome with an estimated incidence of 4 new cases/million population/year.[53] Around 80% of patients are women, with a median age of 40 years at diagnosis. However, the disease may have an earlier onset, since livedo racemosa often goes unnoticed; it is worth noting that in our series, skin semiology was an essential feature in establishing the hereditary nature of the process.[3,4,26,27] A mortality rate of 9.5% is reported in an average observation period of 6.2 years.[7]

In the series by Bottin et al.,[31] comprising 53 consecutive patients with primary SnS, there were 74 strokes: 76% were ischemic strokes, 15% TIAs, and 9% hemorrhagic strokes. Using transthoracic echocardiograms, these French authors found subclinical Libman-Sacks vegetations (see figure 10M)[28] or leaflet thickening in half of the explored patients. The similar incidence of valvular involvement reported here compared to that described in APS-related SnS does not support the hypothesis that such heart valve disorder is due to the presence of circulating aPL antibodies. Another important finding in this series is that the rate of spontaneous abortions, around 30%, is similar to that described in the APS. Thus, the incidence of miscarriage is also not helpful in differentiating primary SnS from other variants of the syndrome.

Regarding imaging studies, for this update I will focus on what has been provided by MRI scans, which were not available at the time of our original descriptions.[3,4] For this purpose, I have selected four primary SnS series, including a total of 135 patients, which provide magnificent brain MRI illustrations.[31,56,61,63] In brief, MRI was systematically abnormal, showing multiple cortical-subcortical and cerebellar non-territorial infarcts accompanied by a variable degree of brain atrophy. There may be widespread white matter changes,[55] which, if the extensive vascular pathology is not taken into account, may be mistaken for the white matter degeneration seen in familial leukodystrophies.[45] The small cortical infarcts observed in our autopsy study (see Figure 10E, L)[28] have been elegantly illustrated by Yilmaz et al.[63] in FLAIR and T2-weighted images (see their figure 4).

Our initial proposal that primary SnS may have a genetic basis has largely been confirmed, with transmission being either autosomal dominant or autosomal recessive.[44,57,64-66] Exceptionally, recessive loss-of-function mutations of *CECR1*, encoding ADA2, a growth factor that is the major extracellular adenosine deaminase, were associated with a spectrum of vascular and inflammatory phenotypes, some of them mimicking primary SnS.[67-70] Greisenegger et al.[71] performed whole-exome sequencing of two affected siblings, aged three months and five years, belonging to a consanguineous family with primary SnS, and identified a homozygous *NOTCH3* mutation within the epidermal growth factor repeat 19. The relevance of these genetic features calls for future studies analyzing large series of well-defined primary SnS in adulthood.

In relation to dermatopathology, immunohistochemical studies have enabled the identification of sequential changes in small- to medium-sized arteries of the dermis-subcutis, ranging from initial endotheliitis to late fibrosis and shrinkage of the affected vessels.[22,23] Cells involved in subendothelial proliferation were positive for vimentin and actin, which are specific to smooth muscle and mesenchymal cells, thus confirming our histological findings in the digital arteries (see Figure 7).[4] The proposition that SnS represents an immune-mediated disorder, as proposed by Sepp et al.,[23] remains to be proven, as this has not been demonstrated in later and more detailed necropsy studies (see above).

Focusing on primary SnS, the optimal treatment remains an unsolved issue, with most authors recommending antiplatelet agents and the avoidance of vascular risk factors.[6-8]

I would like to end with an artistic reference. As noted by Stenager,[72] a very important part of neurological examination is the ability to observe, which is not unique to neurology but is also needed in other professions, such as describing and interpreting art, including portraits. The vision of a livedo racemosa generalisata (see Figure 2)[4] constitutes, in my personal appreciation, a powerful reason for any painter to capture it. Well, in 2018, visiting the Collection of the Russian Museum in Malaga, I came across the portrait of a young woman (*Artist's model*) by Vladimir Lebedev illustrating a case of livedo generalisata, particularly visible on the model's thighs (Figure 11).[73]

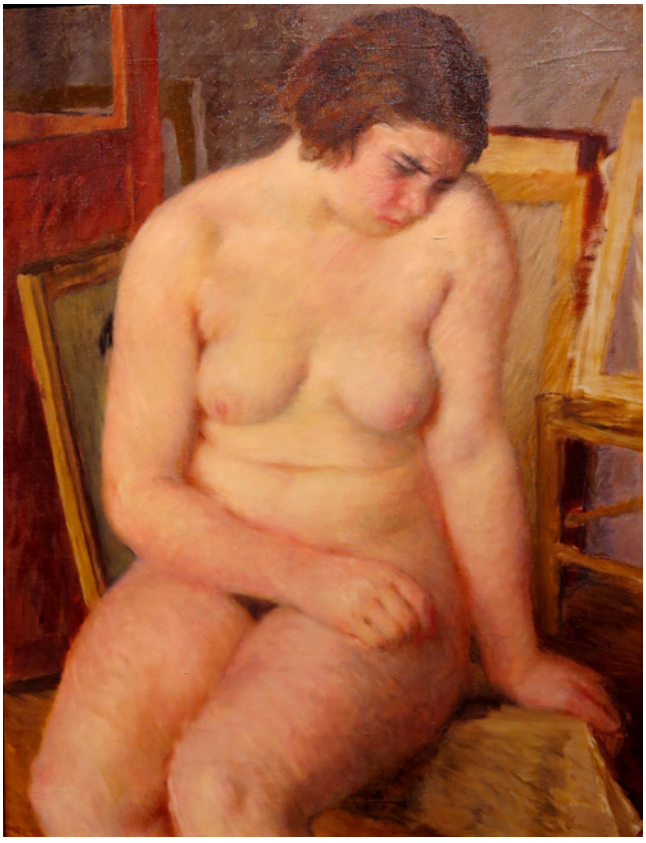

Figure 11. *Artist's model* by Vladimir Lebedev (Oil on canvas, 76.8 × 60 cm; original painted around 1930). Photograph taken by the author. Note the presence of livedo racemosa generalisata. Reproduced with kind permission from the State Russian Museum (Saint Petersburg, Russian Federation). Taken from Berciano.[73]

Conclusions

Our prospective clinical-pathological study of eight presumptive cases of primary SnS and literature review allow us to suggest that this syndrome represents a new form of genetic, progressive, occlusive, non-inflammatory arteriopathy, which mainly involves medium-sized vessels. Primary SnS, cerebral thromboangiitis obliterans, and Divry–van Bogaert syndrome should probably be considered as a single nosological entity.

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Conflicts of interest

The author has no conflicts of interest to declare. This study has received no public or private funding.

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