

Sneddon síndrome. A case presentation and review of key points

Síndrome de Sneddon. Presentación de un caso y aspectos clave

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Summary

SNEDDON syndrome (SS) is a rare, non-inflammatory thrombotic vasculopathy characterized by the combination of cerebrovascular disease and livedo reticularis (LR). The estimated incidence of SS is 4/1,000,000 per year in the general population and usually occurs in women between the ages of 20 and 42 years. For the diagnosis of SS, skin biopsy and abnormal findings on neurological examination and/or magnetic resonance imaging (MRI) are mainly taken into account. Among these latter findings, it is important to highlight the presence of nonspecific multiterritorial infarcts and cortical atrophy and, less frequently, hemorrhagic changes such as cerebral microbleeds. Angiography may reveal stenosis or occlusion of medium and large arteries and extensive networks of small collateral vessels. Previous retrospective studies on the course of the disease have revealed a wide range of neurological symptoms. We present the case of a 48-year-old woman with SNEDDON syndrome, characterized by multiple recurrent ischemic events, livedo reticularis, history of two spontaneous abortions, hypertension, progressive neurological deterioration, and a confirmed mutation of the *CECR1* gene (22q11.2), who underwent a brain MRI that showed old infarcts in the bilateral centrum semiovale and basal ganglia, as well as microbleeds in the brainstem, among others. This case highlights the importance of considering SS in young patients with a history of recurrent cerebral ischemia and livedo reticularis.

Key words (MeSH)

Sneddon syndrome
Vasculopathy
Thrombosis
Magnetic resonance imaging

Palabras clave (DeCS)

Síndrome de Sneddon
Vasculopatías
Trombosis
Resonancia magnética

Resumen

El síndrome de Sneddon (SS) es una vasculopatía trombótica no inflamatoria rara caracterizada por la combinación de enfermedad cerebrovascular con livedo reticular (LR). Se estima que la incidencia del SS es de 4/1.000.000 por año en la población general y suele ocurrir en mujeres entre los 20 y 42 años de edad. Para el diagnóstico del SS se tienen en cuenta principalmente la biopsia de piel y hallazgos anormales en el examen neurológico o en la resonancia magnética (RM), como infartos multiterritoriales no específicos y atrofia cortical; con menor frecuencia, cambios hemorrágicos como microhemorragias cerebrales. En angiografía se puede encontrar estenosis u oclusión de arterias de tamaño mediano y grandes redes de pequeños vasos colaterales. Estudios retrospectivos previos sobre el curso de la enfermedad revelaron una amplia gama de síntomas neurológicos. Se presenta el caso de una mujer de 48 años con síndrome de Sneddon, caracterizado por múltiples eventos isquémicos recurrentes, livedo reticular, antecedentes de dos abortos espontáneos, hipertensión arterial, deterioro neurológico progresivo y una mutación confirmada del gen *CECR1* (22q11.2), a quien se le realizó una RM cerebral que evidenció infartos antiguos en centros semiovales y ganglios basales de forma bilateral, así como microhemorragias en el tallo cerebral, entre otros. Este caso destaca la importancia de considerar el SS en pacientes jóvenes con antecedentes de isquemia cerebral recurrente y livedo reticular.

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Introduction

Sneddon syndrome (SS) is a rare disorder. The incidence of SS is estimated to be 4/1,000,000 per year in the general population and usually occurs in women between the ages of 20 and 42 (1). The diagnosis of SS is mainly based on skin biopsy and abnormal findings on neurological examination or magnetic resonance imaging (MRI) (2). Among the latter findings, it is important to highlight the presence of nonspecific multiterritorial infarcts and cortical atrophy characterized by neurological and dermatological manifestations caused by ischemic cerebrovascular disease and generalized livedo reticularis (3). It can affect other organs, such as the heart, kidneys, eyes, and peripheral nerves, in many cases in relation to concomitant systemic hypertension. This disorder affects small to medium-sized arteries at the border of the dermis and subcutaneous tissue (4). It is crucial to be aware of SS due to its rarity and clinical complexity, its close association with ischemic cerebrovascular events, and the need to differentiate it from other similar pathologies. Accurate diagnosis is essential to guide appropriate treatment and explore potential therapeutic options, which can significantly improve the prognosis and quality of life of affected patients.

Case description

This is a 48-year-old female patient who consulted for headache, paresthesia in the left side of her body, and hearing loss. She had a history of recurrent ischemic events for six years, hypertension since age 16, and two spontaneous abortions (G4A2V2); her family history included cerebral aneurysm in her mother and familial hypertension. Physical examination revealed livedo reticularis (Figure 1), gait with increased polygon of support, difficulty walking on tiptoes and heels, mild left dysdiadocokinesia, and left dysmetria, with preserved strength and osteotendinous reflexes. Subsequently, an audiometry test was performed, which showed mild to moderate bilateral sensorineural hearing loss. A brain MRI was performed with the following findings: areas of high signal intensity on T2-weighted sequences in the white matter, likely related to small vessel disease, old infarcts in the semioval centers and bilateral basal ganglia, microhemorrhages in the brainstem, and greater than expected cortical volume loss for her age (Figure 2). Due to high clinical suspicion, a genetic test was performed, which revealed a mutation in the *CECR1* gene (22q11.2). These findings in the patient are consistent with Sneddon syndrome.

Discussion

In 1959, Kimming described the association between livedo reticularis and cerebrovascular manifestations (4). Subsequently, in 1960, Champion and Rook described a case of diffuse occlusive arterial disease and cerebral ischemia associated with a skin condition (5). Five years later, in 1965, Ian Sneddon was the first author to report on six patients with severe, generalized bluish discoloration of the skin (also called livedo reticularis) and "multiple cerebrovascular incidents of a limited and benign nature," thus describing the syndrome that now bears his name (6).



Figure 1. Image of the patient's physical examination. A persistent erythematous/violaceous reticular or "net-like" pattern is observed in the upper third of the legs (thighs), consistent with livedo reticularis.

According to Schellong et al., cited by Wu S. et al. (1), three forms of the syndrome have been described: the first is idiopathic; the second involves antibody-mediated autoimmunity, with a link to antiphospholipid antibodies or coexistence of systemic lupus erythematosus (SLE) or lupus-like disease; and, finally, a thrombophilic form (1). The three etiological forms of the syndrome described by Schellong et al. have different pathological manifestations. The idiopathic form, by definition, lacks identifiable specific pathological findings that explain the disease, so the diagnosis focuses on ruling out other causes. In the antibody-mediated autoimmunity form, if it is related to antiphospholipid antibodies (as in antiphospholipid syndrome) (1), the central pathology is vascular thrombosis (arterial, venous, or small vessel) or obstetric morbidity, with possible endotheliosis or non-inflammatory thrombotic vasculopathy. If autoimmunity is associated with systemic lupus erythematosus or similar diseases, the pathological findings are more varied and include vasculitis, immune complex deposits in various tissues (such as the kidney or skin), tissue inflammation, and possible secondary fibrosis; lupus nephritis and interface dermatitis are characteristic examples. Finally, the thrombophilic form manifests pathologically with thrombi in arteries or veins due to underlying hypercoagulability, which can lead to vascular occlusion, ischemia, and infarction in the affected organs without primary inflammation of the vessel wall, unless it is secondarily induced by the thrombus.

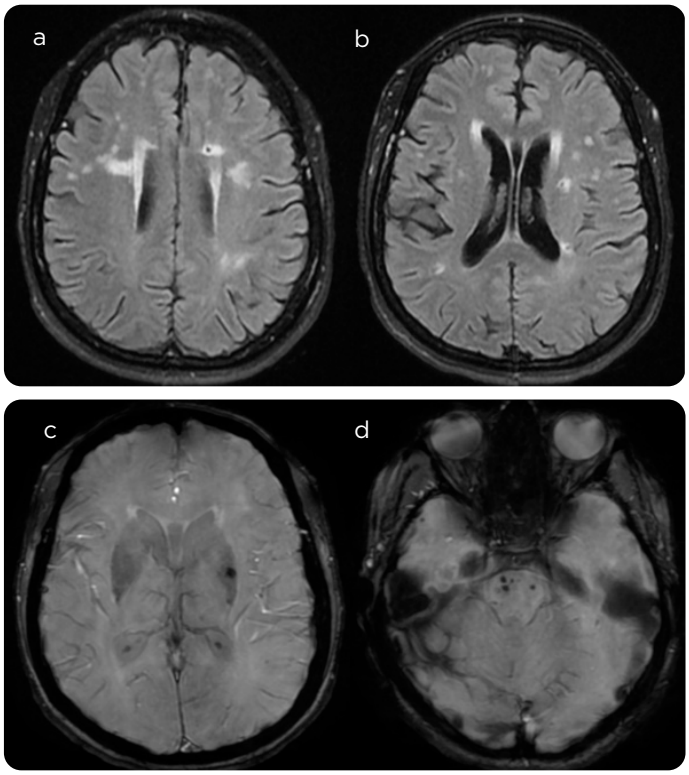


Figure 2. a and b) Brain MRI, FLAIR sequence with T2 information in the axial plane. High signal in the bilateral periventricular white matter and in the semioval centers, findings consistent with small vessel disease, without mass effect. c and d) Brain MRI, SWI sequence (with magnetic susceptibility). Low signal (hypointense) punctate foci in the basal ganglia (c) and pons (d), corresponding to microhemorrhages.

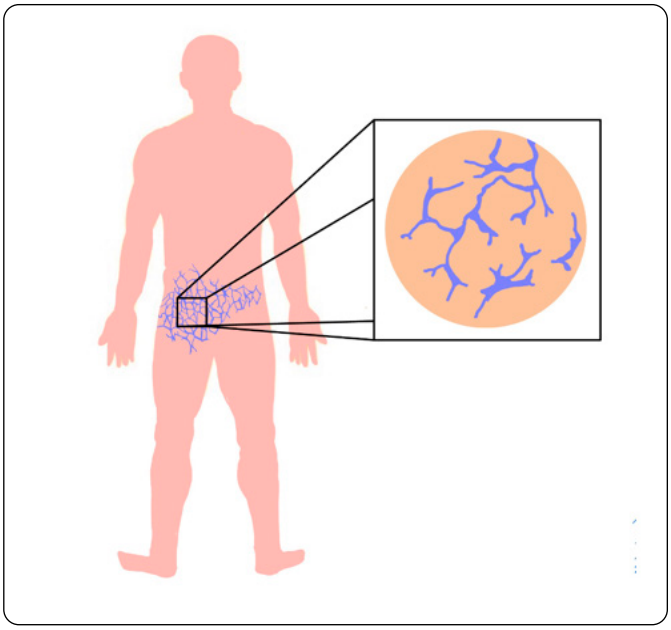


Figure 3. Livedo reticularis (LR). Diagram showing an irregular network-like skin pattern, ranging in color from erythematous to dark purple (cyanotic). It is usually located mainly on the trunk, covering the gluteal region and lower back. Prepared by Sara Gómez Milanés.

It generally occurs sporadically. However, there are records of some cases of patients with a family history (7). Rebollo et al. described familial cases with an autosomal dominant pattern and complete or incomplete penetrance (8). Similarly, Hademenos et al. indicated in a review on the genetics of cerebrovascular diseases and strokes that SS is inherited in an autosomal dominant manner; however, they did not refer to a known type of gene involved (9).

For their part, Zhou and Navon Elkan identified de novo mutations in the *CECR1* gene (chromosomal region of cat eye syndrome), which encodes ADA2 (10), as the cause of a syndrome that includes systemic vasculopathy and inflammation. Subsequently, Bras et al., cited by Wu S. et al. (1) expanded the phenotypic spectrum of ADA2 deficiency to include a familial form of SS (1).

In this case, diagnostic criteria are available which, although still evolving, are used in clinical practice. The diagnosis is generally established through a combination of suggestive clinical manifestations such as vasculopathy (livedo, cerebral infarcts, polyarteritis nodosa), systemic inflammation, immunodeficiency, and/or hematological abnormalities, together with confirmatory laboratory tests. These confirmatory tests are crucial and include demonstrating low or absent levels of ADA2 enzyme activity in serum or plasma and, definitively, identifying pathogenic biallelic mutations in the *CECR1* (ADA2) gene through genetic analysis.

One of the manifestations of SS, as mentioned above, is livedo reticularis, which is defined as an irregular net-like pattern on the skin, ranging in color from erythematous to dark purple (cyanotic); it is characterized by being a persistent lesion that is not influenced by temperature. It is usually located mainly on the trunk, covering the gluteal region and lower back, and then extends to the extremities, along the thighs and upper arms (5, 6). This finding can be observed before cerebrovascular events occur in more than 50% of cases; in certain patients, this skin pattern is first identified when the stroke occurs, while in less common situations, livedo reticularis appears after neurological symptoms. In addition to this entity, some patients show signs of Raynaud's phenomenon in the hands and feet, and others show generalized mottled purple skin discoloration, which has been diagnosed as systemic angiomatosis (Figure 3).

Skin manifestations in adenosine deaminase 2 deficiency (DADA2) are heterogeneous and reflect the underlying systemic vasculopathy. Livedo reticularis or racemosa is one of the most common presentations, observed in approximately 40-60% of patients, and may precede cerebrovascular events in most of these cases. Other manifestations include Raynaud's phenomenon, present in about 10-20% of individuals, and less common forms such as generalized purplish mottled skin discoloration, sometimes diagnosed as systemic angiomatosis. Although the severity of these skin changes varies, their presence, being indicative of the systemic vasculopathy inherent in DADA2, correlates with an increased risk of vascular involvement in other organs, including the central nervous system. Although the direct relationship between the specific severity of peripheral skin lesions and the magnitude of cerebral findings is not always linear, the coexistence of these manifestations underscores the multisystemic nature of the disease and the propensity for generalized vascular complications (12).

Skin biopsy is essential for early diagnosis of SS. It can reveal thrombosis of subcutaneous arterioles and compensatory dilation of capillaries with blood stasis, which causes the known dermatological manifestation. The pathogenesis involves a stepwise progression from initial endotheliitis to vascular fibrosis. Although biopsies may show different pathological phases, clinical severity does not always correlate with histological findings, which makes them less specific. Deeper biopsies increase diagnostic sensitivity from 27% with one biopsy to 53% with two biopsies and 80% with three biopsies taken from white areas in most cases (13).

In neurological manifestations, stroke plays a key role, usually caused by ischemia (transient ischemic attacks and cerebral infarction) in the perfusion areas of the middle cerebral artery or posterior cerebral artery. Common symptoms include hemiparesis, sensory disturbances, aphasia, and visual defects, although most strokes are mild; migraine headache is a common symptom in about 50% of patients (14). Cognitive impairment and psychiatric disorders affect approximately 77% of patients with SS, with concentration, attention, memory, visual perception, and visuospatial construction being the most commonly described cognitive dysfunctions; over time, dementia may even develop in young patients. Focal or generalized seizures are common, while intracerebral hemorrhages are rare. Over the years, patients develop cognitive dysfunction and then dementia due to the cumulative effects of multiple cerebral infarcts and even psychiatric conditions such as the onset of depressive episodes, although the latter can manifest without prior stroke. Movement disorders, such as chorea and tremor, are rare but have been described, as is intracerebral, subarachnoid, or intraventricular hemorrhage (1).

Pathological results in brain biopsies show multiple vascular thromboses without other signs of vasculitis (1), and another biopsy report linked it to cortical infarcts and leukoencephalopathy, along with intimal fibrosis in the basal vessels (8). A postmortem study

(16) revealed diffuse vasculopathy affecting small- to medium-sized arteries, including cerebral arteries, with proliferation of the intima and media, and some arteries showed fibrotic occlusion and recanalization (16). Another case showed multiple cortical infarcts with obstruction of medium-sized arteries and marked smooth muscle hyperplasia in smaller arteries (17). Although a granulomatous reaction in the leptomeninges has been reported, it is not a constant feature of SS (1, 15).

Leptomeningeal involvement in the form of a granulomatous reaction is not considered a pathognomonic or constant feature of SS syndrome (presumably DADA2); however, its occasional presence may have correlates in neuroimaging. Specifically, granulomatous inflammation of the leptomeninges could manifest on brain MRI as focal or diffuse leptomeningeal enhancement after gadolinium administration. The detection of this enhancement pattern, although uncommon, would suggest inflammatory meningeal involvement and should be considered in the clinical context of the patient, although its absence does not exclude the diagnosis of the disease or other more prevalent neurological manifestations associated with the underlying vasculopathy.

Systemic hypertension, as well as the use of oral contraceptives, correlates with the progression of central nervous system damage (1).

Imaging of the central nervous system plays a key role in the diagnosis of neurological complications. Although this can be done using computed tomography (CT) or MRI, the latter is preferable. While both techniques can identify large and medium-sized infarcts, MRI is not only more sensitive for the early detection of brain lesions and often reveals more extensive and numerous involvement than would be possible to visualize with CT, but it is also more effective in precisely defining the nature, extent, and characteristics of the infarct. Sequences such as diffusion-weighted imaging (DWI) are crucial for confirming acute ischemia in its earliest stages, while other sequences such as FLAIR, T2*, and studies after contrast medium administration allow for better delineation of the affected area, evaluation of edema, identification of hemorrhagic transformations, and estimation of the age of the lesion, which are fundamental aspects for the complete characterization of the ischemic event and its sequelae (2).

Among the most common findings on MRI are chronic infarcts affecting the cortex and subcortical region, as well as cortical atrophy. In addition, it is common for patients to have small, circumscribed lesions in the white matter of the hemispheres, brainstem, and/or cerebellum. These lesions typically manifest as high signal intensity on T2-weighted sequences and, notably, on FLAIR (Fluid-Attenuated Inversion Recovery) sequences; the latter is particularly useful due to its ability to suppress the signal from cerebrospinal fluid and enhance the visibility of these lesions. On T1-weighted images, these lesions usually have a medium or low signal, depending on their chronicity and nature (2).

In this case, high signal intensity was observed in bilateral periventricular white matter and semioval centers on T2 and FLAIR sequences without mass effect or water diffusion restriction. Magnetic susceptibility and T2GE images showed low punctate signal intensity in the pons and medulla, corresponding to microhemorrhages. Small encephalomalacia was also observed in the corpus callosum, as well as greater than expected peripheral subarachnoid space for the patient's age. No alterations in vascular structures or abnormal enhancements were found after contrast administration.

In patients with DADA2 who present with acute neurological symptoms, angiographic studies, including digital subtraction angiography, CT angiography, or MR angiography, may reveal a spectrum of vascular abnormalities such as multifocal arterial stenosis, occlusions, vascular wall irregularities, and occasionally dilations or aneurysms. High-resolution imaging of the vascular wall may also reveal parietal enhancement as a sign of active vasculitis. Complementarily, advanced MRI techniques are crucial: diffusion-weighted imaging (DWI) is essential for the early detection of acute ischemic infarcts, while perfusion-weighted imaging (PWI) can delineate areas of hypoperfusion and ischemic penumbra, and MR spectroscopy (MRS) can characterize metabolic changes in lesions. Beyond the high-signal areas in sequences with information on white matter and the commonly described microhemorrhages, the spectrum of findings in the central nervous system in DADA2 may also include extensive or lacunar acute infarcts with water diffusion restriction on DWI, larger parenchymal hemorrhages, aneurysms (18), unbroken intracranial vessels, arterial stenosis or occlusions visible in MR angiography or CT angiography studies, infrequent leptomeningeal enhancement, and, more rarely, spinal cord involvement, cerebral calcifications, or optic nerve involvement, reflecting the wide phenotypic variability of this systemic vasculopathy (19).

Based on these findings and taking into account the review conducted, it can be concluded that these findings are more commonly found in patients with advanced stages of this pathology, but they are not sufficient to reach a complete diagnosis. The combination of clinical, paraclinical, imaging, and histopathological characteristics is what provides a definitive diagnosis; otherwise, this imaging pattern may raise a high suspicion, but differential diagnoses such as systemic lupus erythematosus, polyarteritis nodosa, cryoglobulinemia, livedoid vasculitis, cold agglutinin disease, arteriosclerosis, and cholesterol embolism (16, 17) on MRI can generate brain lesion patterns that share similarities with those observed in DADA2. Systemic lupus erythematosus and polyarteritis nodosa are also vasculopathies that can cause multiple cerebral infarcts in various areas, white matter lesions, and, occasionally, hemorrhages or aneurysms, findings that significantly overlap with DADA2. Similarly, cryoglobulinemia can induce small vessel vasculitis with consequent infarcts or leukoencephalopathy. Livedoid vasculitis, although predominantly cutaneous, can be associated with cerebral ischemic events in the context of broader syndromes. Cold agglutinin disease can cause occlusion of small vessels and ischemic lesions due to hyperviscosity or intravascular agglutination. Finally, severe arteriosclerosis and cholesterol embolism are common causes of multiple cerebral infarcts, both cortical and subcortical, and chronic ischemic leukoencephalopathy, which can mimic the pattern of cumulative vascular damage seen in some patients with DADA2, especially in older populations or those with vascular risk factors. The distinguishing key often lies in the combination with the clinical presentation, the patient's age, systemic involvement, and, ultimately, the genetic and enzymatic findings specific to DADA2.

The differential diagnoses for neurological symptoms include other diseases such as multiple sclerosis and multiple cardiac embolization, and infections such as syphilis and Lyme disease (1); Central nervous

system (CNS) vasculitis encompasses various diseases that cause inflammation and damage to the blood vessels of the brain, spinal cord, and meninges. It is divided into systemic vasculitis and isolated CNS angiitis, the latter being more common in men over 40 years of age. Histological findings include mononuclear cell infiltrations in the vascular walls (20).

Conclusion

In this case, we present the profile of a patient diagnosed with Sneddon syndrome, a rare disease characterized by livedo reticularis and neurological manifestations. Clinical and imaging findings, specifically CNS MRI, revealed multiple chronic cortical and subcortical infarcts, as well as small, circumscribed lesions in the white matter. These results support evidence of an underlying vasculopathic process, suggesting progressive vascular obstruction and recanalization in the cerebral arteries. The absence of new lesions during follow-up and the stability of qualitative cortical atrophy highlight the importance of careful monitoring in patients with this syndrome. These findings underscore the usefulness of MRI in the evaluation and follow-up of patients with SS, as well as in providing crucial information for the clinical management and prognosis of the disease.

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