Comprehensive insights of Sneddon syndrome: A clinical perspective

Ahmad Yousef Alazzam

Faculty of Medicine, The Hashemite University, Zarqa, Jordan.

Journal of Central Nervous System Disease
Volume 16: 1–7

DOI: 10.1177/11795735241308767

ABSTRACT

BACKGROUND: Sneddon's syndrome is a rare thrombotic vasculopathy characterized by the coexistence of both cerebrovascular events and livedo reticularis.

OBJECTIVE: This review aims to raise awareness among physicians by discussing the whole clinical spectrum of the disease. Typically, Sneddon syndrome presents in middle-aged women with a cerebrovascular accident and a preexisting skin rash, which is livedo reticularis. Diagnosis is primarily clinical, relying on a high index of suspicion. Management focuses mainly on reducing the risk of cerebral infarctions and alleviating symptoms.

CONCLUSION: Further research is necessary to better understand the disease's nature, which will contribute to improving early diagnosis and optimal management.

KEYWORDS: Sneddon syndrome, cerebrovascular disease, livedo reticularis, thrombotic vasculopathy, stroke

RECEIVED: September 4, 2024. **ACCEPTED:** December 2, 2024.

TYPE: Review

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Ahmad Yousef Alazzam, Faculty of Medicine, The Hashemite University, Zarqa 13133, Jordan.
Email: ahmadyousefalazzam@gmail.com

Introduction

Sneddon syndrome (SS) is a rare, non-inflammatory chronic arterio-occlusive disease that affects small to medium-sized arteries, predominantly in Young females. It typically presents with livedo reticularis (LR) and cerebrovascular accidents (CVA).[1]

Historical background

The syndrome was first described by a British dermatologist named Dr Ian Bruce Sneddon, who reported six cases presented with diffuse LR and cerebrovascular lesions in the 1960s. He excluded polyarteritis nodosa, systemic lupus erythematosus (SLE), thrombocythemia,[2] and other arterial etiologies. In the late 1970s, this condition was later named after Dr Sneddon as SS.[3]

Classification

Sneddon syndrom classification remains a controversial topic in literature, the primary classification uses the presence of antiphospholipid antibodies (aPL), which is more commonly used in the literature. it was first identified in 1988 in a case report.[4] In this classification, Group I is considered aPL negative, while Group II is aPL positive with three main antibodies: anticardiolipin, lupus anticoagulant, and anti-beta 2-glycoprotein I.[5] In 1997, another proposed classification divided cases into primary (where there is no obvious etiological cause such as autoimmunity or SLE) and secondary which is linked to autoimmunity or thrombophilia.[6]

Epidemiology

The estimated incidence for SS is four cases per million in the general population, with a particular affinity for women aged 20 to 42 years.[7] The median age of diagnosis is approximately 40 years, according to cohort studies.[8] In a hospital-based series of stroke patients, the frequency of SS is estimated to be between 0.25% and 0.50%. Additionally, a mortality rate of 9.5% has been observed during a mean observation period of 6.2 years.[9] While SS is usually in a sporadic form, familial cases were also reported in the literature.[10-12]

Pathogenesis

The pathogenesis of SS is still a controversial topic in the literature, with multiple theories suggesting autoimmunity, thrombotic disorder, and even familial and genetics. Despite the strong association with aPL, a substantial percentage of patients are aPL-negative, suggesting potential etiological differences among SS cases. While the majority of strokes are not cardioembolic in origin, the thrombotic disorder was discussed, including its association with factor V Leiden, protein S, and C deficiencies,[12,13] which affected half of the patients in one cohort[13-15]

Some researchers have suggested that SS may be an autosomal dominant disorder with variable penetrance, as evidenced by occasional familial cases. Some individuals within these families might have a newly identified autosomal recessive condition linked to a mutation in the cat eye syndrome region, candidate 1 (CECR1), which encodes Adenosine deaminase 2 (ADA2).[16]

Additionally, vascular risk factors are also strongly associated with SS, such as hypertension, smoking, oral contraceptive pills, and others. APL-negative SS patients exhibited at least 2 cardiovascular risk factors in 64% of patients.[14] There is debate surrounding whether Sneddon's syndrome represents a uniform disease with a single pathogenesis or a group of related yet diverse diseases sharing similar clinical features but differing in pathogenesis.

Clinical manifestation

The natural history

Sneddon syndrome (SS) follows a progressive course with different stages, as described by several cohort studies. Stage I is the prodromal phase, which is characterized by headaches (often migraine-like), exacerbated by environmental factors or menstruation. These headaches preceded focal neurological symptoms by a significant duration up to 9 years, and it was not associated with elevated blood pressure. Dizziness may occur before, simultaneously with, or after focal symptoms, all these symptoms may even precede LR. The median period between the onset of neurological symptoms and the diagnosis ranged from 2 to 6 years.[8,17,18]

Stage II is the fully developed disease stage, featuring multifocal symptoms in most patients, with transient ischemic attacks (TIAs) and/or ischemic strokes occurring regardless of prior TIAs. Focal symptoms lasted minutes, recurring variably from weekly to yearly, often identical in 75% of patients. Seizures were usually secondary to focal symptoms, occasionally primary.

Stage III is characterized by progressive cognitive decline, ranging from mild memory loss to severe dementia, and mood disturbances such as depression. Symptoms may manifest early, up to 13 years before initial focal signs.

Neurology

Neurological involvement is one of the hallmarks of SS either in the form of stroke or transient ischemic attacks (TIAs), other neurological manifestations such as headache, seizures, cognitive impairment, psychiatric disturbances, and nonspecific symptoms were reported.

It was reported that 76% of strokes in patients with SS are ischemic in origin mostly due to superficial Middle cerebral artery (MCA) occlusion followed by deep MCA then posterior cerebral artery and cerebellar arteries, the main presenting symptoms was sensorimotor dysfunction (hemiparesis) followed by cortical dysfunction (aphasia, hemianopia).[14,19] TIAs typically precede the occurrence of major CVA in these patients.

Hemorrhagic stroke, though rare, accounting for only 9% of total strokes, but still frequently reported as intracranial hemorrhage (ICH), intraventricular hemorrhage (IVH), subarachnoid hemorrhage (SAH), and subdural hematoma (SDH).[20-22] The mechanism is vague but most likely due to narrowing or blockage of medium to small-sized intracranial arteries, and occasionally, the presence of leptomeningeal and transdural collateral networks.

Headache is one of the nonspecific symptoms in neurology; in the context of SS; accompanied headache has a strong association with SS, in the available cohorts, more than half of the patients had experienced headache,[14,23] additionally, migraine was linked to LR and the risk of strokes in multiple studies.[24,25] Even more severe forms of disabling headaches were reported.[26]

Impaired cognition has been reported in SS, even reported as the first clinical presentation, however, it may be confused with Divry van Bogaert Syndrome (DBS) which also has LR and dementia.[27]

Dementia in SS is rare and may mimic Alzheimer's disease, posing diagnostic challenges. In approximately half of cases, dementia in SS develops following a transient cerebral event. Cognitive deficits in SS may affect concentration, attention, memory, and visual perception. SS patients may also experience psychiatric symptoms like suicide attempts and psychosis, thought to be related to the syndrome. Occasionally, dementia and mood disorders arise without prior neurological deficits, potentially linked to silent stroke.[28,29]

Seizures and epilepsy are also linked to SS, either secondary to CVA or as the first presentation, as reported in one case report[30] Moreover, tremors and other movement disorders were associated with SS.[16]

Dermatology

The second hallmark for SS is Livedo reticularis (LR) as described by the original Sneddon's paper, LR is defined as a skin condition that presents as a temporary or persistent, mottled, reddish-blue to purple, net-like cyanotic pattern. It reflects disruption of the cutaneous blood flow and can be seen in numerous physiological and pathological conditions.[31] The distribution of LR can vary between patients but is almost universal in the limbs (especially legs) followed by the trunk and/or buttocks.[5,14]

Livedo reticularis precedes stroke in almost half of the patients, while in others, it appears around the time of the first cerebrovascular event or afterward. In the European literature, they describe livedo racemosa (LRC) instead of LR, although each one has its own characteristics. Historically, the skin changes seen in Sneddon's syndrome have been referred to as LR. However, LR is seldom linked with the early skin stages of SS. LR is typically a physiological process, rarely related to a

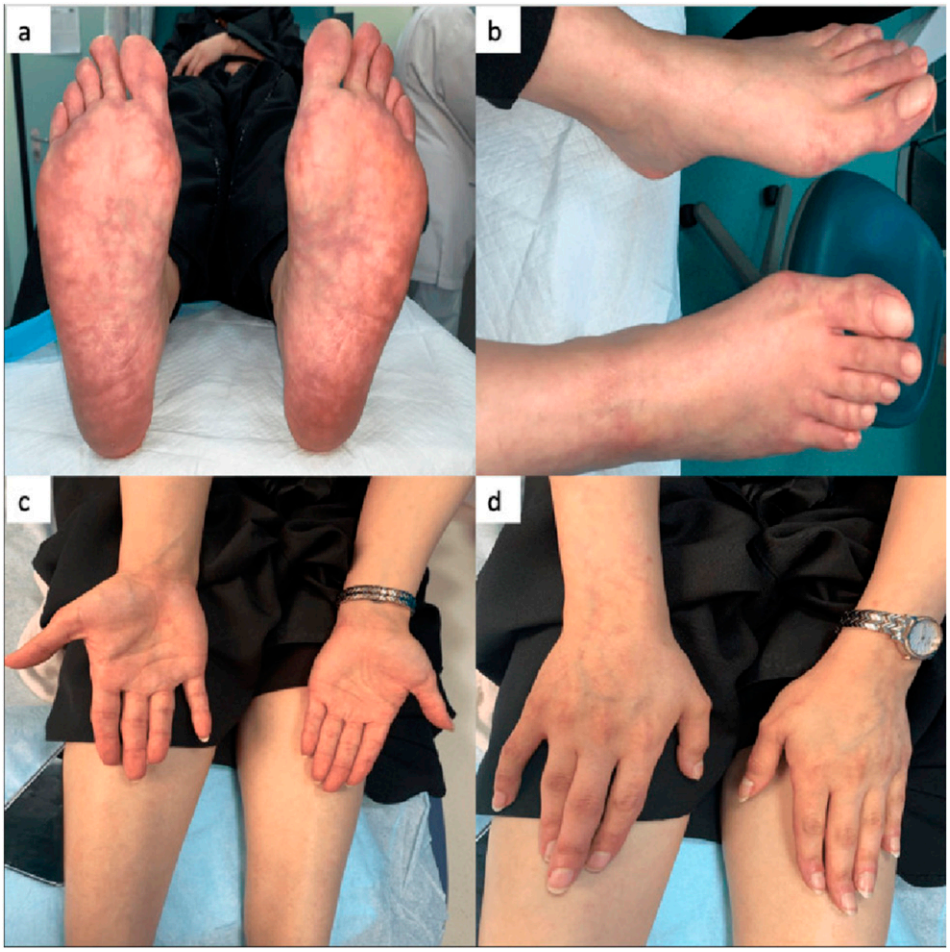

Image 1. Multiple erythematous-to-violaceous irregular reticular patterns with incomplete circular patches (livedo racemosa) livedo racemosa. *Sneddon Syndrome: A Case Report from Saudi Arabia. (2023).*

pathological condition, and it usually presents as more symmetrical and uniform. Both LR and LRC are thought to be signs of disturbances in the skin's blood flow. However, LRC is almost always pathological and is usually a secondary symptom of disorders such as SS or Antiphospholipid Syndrome (APS). Unlike LR, LRC is permanent and tends to have a more generalized and widespread appearance.[1,31] Image 1 represents livedo racemosa on both the plantar and dorsal aspects of foots as well as the palmar and dorsal aspects of both hands.[32]

Raynaud's phenomenon is also reported in many patients even as a principal sign involving the fingers and toes.[33] Acrocyanosis,[34] which is a constant condition has also been documented along with angiomatosis in some patients.

Ophthalmology

Multiple and wide range of ophthalmological conditions were reported in SS, including central artery occlusion, central vein occlusion,[35-38] unilateral third nerve palsy,[39] homonymous hemianopia,[40,41] intraocular ophthalmoplegia,[42] optic disc microaneurysm and macular edema,[43] retinal neovascularization,[44] Optic nerve infarction[45] and other rare conditions. However, central vein occlusion is the most common complication between them.

Cardiac manifestations

Cardiac involvement in SS often includes valvular and myocardial lesions. Valvopathy is more significant especially in aPL-positive patients due to fibrosis and damage to the valves that leads to the formation of a thrombus and increases the risk of stroke.[46]

The mitral valve is most frequently affected followed by the aortic valve. Indeed, Clinical examination and transthoracic echocardiography should be regularly performed.[47] Furthermore, acute transmural myocardial infarction due to LAD occlusion,[48] cardiac vasculopathy,[49,50] and others were reported. Also, complications and challenges during surgeries are reported like Obstructive valve thrombosis after transcatheter aortic valve replacement.[51]

Hypertension is also associated with SS, the prevalence ranges from 22.5% to 60%,[14] in rare circumstances end-organ damage occurs, Hypertension is the only risk factor significantly associated with a more severe course of the disease.[52]

Extracranial vaso-occlusive events

Extracranial vaso-occlusive events documented in up to 24% in aPL-negative patients, impacting arteries such as Digital artery, superior mesenteric artery, and renal arteries, along with venous thromboses including deep venous thrombosis and pulmonary embolism.[19,53] The prevalence of these vascular event is 19% in both aPL-negative and aPL-positive patients.[14] A recent case report of cerebral venous sinus thrombosis in an aPL-negative women, further highlighting the variability of vascular complications in SS.[54]

Renal system

Renal involvement in SS typically manifests as slight elevation in serum creatine and blood urea nitrogen (BUN) along with decreased creatinine clearance was reported in retrospective studies,[9] with unclear pathophysiology, though it is most likely linked to microvascular nephropathy A few cases have been reported, including two cases of nephropathy[55] and one case of chronic kidney disease (CKD) from membranous nephropathy.[56]

Antiphospholipid syndrome

Antiphospholipid syndrome is the most common acquired thrombophilia, is characterized by thrombosis or pregnancy complications alongside persistently positive aPL antibodies. These antibodies, including aCL, lupus anticoagulant, and beta2-glycoprotein. Multiple studies implicated the association between aPL and SS, a recent cohort reported 32%[14] while the percentage could reach up to 80%.[57] However, in some cases, no antibodies are detected. These antibodies likely play a role in SS pathogenesis, with some experts considering SS and APS as synonymous entities.

Laboratory studies

When considering laboratory tests for patients suspected of having Sneddon's syndrome (SS), it is advisable to encompass pathways implicated in the theorized pathogenesis. This involves a sequential approach: commencing with general tests, secondary vascular risk factors, autoimmune antibodies, thrombotic profile, and Inflammatory, and immune complex deposition, which should also be considered. CSF analysis is usually not required. Labs are summarized in Table 1.[9,14,16,23]

Imaging studies

In the context of neuroradiology, multiple modalities are available, such as magnetic resonance imaging (MRI), computed tomography (CT) scan, CT angiography, MRI diffusion, etc. Brain MRI is more effective than CT scan in detecting small infratentorial infarctions, while CT is better for identifying large territorial strokes and acute intracranial hemorrhages. Diffusion-weighted imaging MRI is sensitive to acute stroke, and susceptibility-weighted imaging is ideal for detecting microbleeds.

One retrospective study Suggested a method to classify cerebral infarcts into 3 main groups in SS, they proposed the following method: large territorial cortico-subcortical, small (2 gyri or less) distal cortico-subcortical, or small deep infarcts (less than 15 mm). Additionally, further classification into either territorial or non-territorial, as well as the presence of white matter lesions or cerebral atrophy.[13]

In one retrospective study in 2021, the pathognomonic pattern of MRI imaging involved numerous cortical-subcortical medium to small-sized infarcts, accompanied by non-territorial infarcts in the cerebellum, amidst mild diffuse and focal cerebral atrophy.[58]

White matter abnormalities were almost universal, primarily in the supratentorial region, while cortical and/or subcortical atrophy was widespread, displaying a diffuse pattern. Meanwhile, lacunar infarcts are rare.[8,23,59]

Correlations between territorial infarcts and cortical/subcortical atrophy, as well as between white matter abnormalities and atrophy, were significant but moderate or modest.[59]

Cerebral angiography is abnormal in up to 75% of patients with SS, the arteriopathy is confined to the third-order vessels and it's not required for diagnosis, The most common abnormality is an obliterating noninflammatory arteriopathy with stenosis and/or occlusion of intracranial vessels.[9,58]

Other imaging studies such as carotid artery Doppler, cardiac echocardiogram, and cardiac MRI are beneficial for the

Table 1. Laboratory studies in suspected SS patients.

General tests	Complete blood count (CBC), blood urea nitrogen (BUN), electrolytes, and kidney function tests (KFT)
Vascular risk factors	Hemoglobin A1C (HbA1C), lipid profile, and proteinuria
Autoimmune antibodies	Antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), and anti-double-stranded DNA (dsDNA)
Thrombotic profile	Factor V, protein S, protein C, prothrombin, antithrombin III, and aPL antibodies, prothrombin G20210A; homocysteine level methylenetetrahydrofolate reductase (MTHFR) mutations
Inflammatory markers	C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)
Immune complex deposition	Complement components C3, C4; CH50 activity

detection risk for thrombosis, valvular abnormalities, endocardium scar or autoimmunity, or any complication reported for SS as discussed.

Differential diagnosis

The differential diagnosis of SS will be discussed from several aspects, firstly LR and LRC, one study suggested an algorithm for both, LR can be classified into Physiological (cutis marmorata (primary, idiopathic, and amantadine-induced LR While LRC is nearly pathological and is a classical sign of Sneddon's syndrome, it is also observed in various other conditions including livedoid vasculopathy, antiphospholipid syndrome (APS), systemic lupus erythematosus (SLE) with or without APS, essential thrombocythemia, thromboangiitis-obliterans, polycythemia Vera, and polyarteritis nodosa.[31]

Secondly, stroke in young adults is uncommon in clinical settings, necessitating a complete assessment to be performed, there are enormous causes and risk factors such as Carotid artery dissection, Antiphospholipid syndrome, Illicit drug use, malignancy, pregnancy, reached up to 90 cause and risk factor as mentioned in this study.[60]

The presence of livedo racemosa (LR) and recurrent strokes is also a feature of Divry van Bogaert Syndrome (DBS), a familial juvenile-onset disorder characterized by LR, white matter disease, dementia, epilepsy, and angiographic findings of "cerebral angiomatosis". Unlike SS, DBS exhibits distinct characteristics, including typical angiographic features of angiomatosis, a hereditary trait, and a juvenile onset of cognitive impairment and leukoaraiosis.[61]

Diagnosis

The Diagnosis of a patient with SS requires a high index of suspicion followed by extensive laboratory and imaging studies such as brain MRI and angiograph. The presence of aPL aids in diagnosing SS in cases with concurrent APS, although approximately 50% of SS patients are aPL-negative the presence of the imaging findings altogether in a young woman without significant risk factors should always lead us to the diagnosis of Sneddon's syndrome.[17]

Magnetic resonance imaging and skin biopsy were employed to confirm Sneddon's syndrome diagnosis. While magnetic resonance findings lacked specificity, they were highly sensitive in detecting asymptomatic brain lesions, facilitating diagnosis in patients with transient symptoms. Skin biopsies displayed characteristic histological features when appropriate techniques were utilized.[62]

Skin biopsies showing at least one artery in the deep dermis with a thickened vessel wall and recanalization or neovascularization can help differentiate Sneddon's syndrome from isolated livedo racemosa, with a sensitivity of 70% and specificity of 69%. Although occluded vessels are less frequently observed and cannot be the primary diagnostic criterion for SS, the presence of a livedo pattern in the superficial dermis may boost diagnostic specificity to 92%, offering a promising new indicator for SS diagnosis.[63]

Management

To date, no prospective randomized trial has been done and no clinical recommendations have been developed for the management of patients with SS. The main approaches to the treatment of SS are individualized by controlling modifiable risk factors and pathophysiological assumptions.

Different treatment strategies are proposed for arterial thrombosis in aPL-positive patients based on individual risk profiles. Elderly patients with low-titer aCL antibodies on a single test may receive low-dose aspirin (LDA) alone. Conversely, patients with high-risk aPL antibody profiles should receive vitamin K antagonists (VKA) with an international normalized ratio (INR) range of 2.0 to 3.0, with or without LDA, or VKA with an INR range of 3.0 to 4.0. The former regimen is generally preferred.[64]

While aPL-negative patient management is debatable, both antiplatelet agents (aspirin and clopidogrel) and anticoagulants (warfarin) have similar effectiveness in preventing the recurrence of cerebral events. However, antiplatelet agents have a better safety profile with a lower risk of bleeding compared to warfarin.[19,65] Under therapy, the global ischemic recurrence rate (including cerebral infarcts, TIAs, and silent infarcts) is less than 30% after 6.5 years of follow-up. Furthermore, treatment interruptions were linked to an increased risk for ischemic events.[66]

Despite the high risk of intracranial bleeding, thrombolysis may be considered a therapeutic option in acute ischemia settings in patients with SS.[65]

Anti-inflammatory drugs, corticosteroids, and immunosuppressive drugs are inefficient,[67] a recent case report in a-PL negative women who received monthly intravenous cyclophosphamide therapy, reported subjective and objective improvement of her neurological and cognitive symptoms.[68] Further trials should be done to address the safety and efficacy.

Several agents have been utilized to treat dermatopathology, including skin ulcers, by reducing blood viscosity and enhancing blood flow. These agents include rivaroxaban ,immunoglobulin, nifedipine, Bosentan, and prostaglandin E1 (alprostadil).[16,59,69,70]

Prognosis

Modified Rankin score (mRS) was used in literature to determine the degree of disability after stroke in SS patients with different outcomes between studies but generally favorable outcomes, in the latest reported cohort with 80% of patients having an mRS ≤2 after 6.5 years.[13] Meanwhile Fetoni et al[71] reported a mortality or severe disability of 60%, while Zelger et al[18] reported 25% mortality or severe disability.

On the other hand, the cognitive prognosis for SS is worse and more progressive compared to other nonprogressive conditions, such as cardioembolic strokes and strokes associated with hematological diseases in young adults.[16,71]

Conclusion

In conclusion, SS is a multi-systemic disease that affects the generalized vascular bed not only the central nervous system, the disease may present with diverse and wide signs and symptoms, but mainly LR and TIAs episodes, the management of SS is a point of controversy that should be tailored case by case, due its nature the prognosis can be poor especially if the cognitive function is affected.

Author contributions

Ahmad Yousef Al-Azzam: Conceptualization; Methodology, Project administration; Resources; Supervision; Writing - original draft; Writing - review & editing.

ORCID iD

Ahmad Yousef Alazzam https://orcid.org/0000-0001-9291-8748

REFERENCES

1. Kong SS, Azarfar A, Bhanusali N. Sneddon syndrome: under diagnosed disease, complex clinical manifestations and challenging diagnosis. A case-based review. *Rheumatol Int*. 2021;41(5):987-991. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85086337331&doi=10.1007%2Fs00296-020-04625-1&rtnerID=40&d5=42490b5ecf8a1fe27c8f516b65c9ead7
2. Sneddon IB. Cerebro-vascular lesions and livedo reticularis. *Br J Dermatol*. 1965;77:180-185.
3. Tanager B. Recurrent transient global amnesia in a case with cerebrovascular lesions and livedo reticularis (Sneddon Syndrome) E. *J Neurol*. 1979;131:2006-2007.
4. Levine SR, Langer SL, Albers JW, Welch KM. Sneddon's syndrome: an antiphospholipid antibody syndrome? *Neurology*. 1988;38(5):798-800.
5. Francès C, Papo T, Wechsler B, Laporte J-L, Biousse V, Piette J-C. Sneddon syndrome with or without antiphospholipid antibodies: a comparative study in 46 patients. *Medicine*. 1999;78(4):209-219. https://journals.lww.com/md-journal/fulltext/1999/07000/sneddon_syndrome_with_or_without_antiphospholipid.1.aspx
6. Schellong SM, Weissenborn K, Niedermeyer J, et al. Classification of Sneddon's syndrome. *Vasa*. 1997;26:215–221. https://pubmed.ncbi.nlm.nih.gov/9286155/
7. Elmahi H, Mernissi FZ. Sneddon syndrome. *Pan Afr Med J*. 2019;34:9.
8. Starmans NLP, van Dijk MR, Kappelle LJ, Frijns CJM. Sneddon syndrome: a comprehensive clinical review of 53 patients. *J Neurol*. 2021;268(7):2450-2457. doi:10.1007/s00415-021-10407-x
9. Wu SJ, Xu ZQ, Liang H. Sneddon's syndrome: a comprehensive review of the literature. *Orphanet J Rare Dis*. 2014;9:215. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85017330286&doi=10.1186%2Fs13023-014-0215-4&rtnerID=40&d5=afcc688e5c232a3a57f818fcd320d887
10. Tily H, Banki K, Hoffman GS, Perl A. Detection of lupus anticoagulant and successful anticoagulation in familial Sneddon syndrome. *Ann Rheum Dis*. 2010;69:775–776.
11. Llufriu S, Cervera A, Capurro S, Chamorro A. Familial Sneddon's syndrome with microbleeds in MRI. *BMJ Case Rep*. 2009;2009:bcr2007131912.
12. Greisenegger EK, Llufriu S, Chamorro A, et al. A*NOTCH3*homozygous nonsense mutation in familial Sneddon syndrome with pediatric stroke. *J Neurol*. 2021;268(3):810-816.
13. Bottin L, Francès C, De Zuttere D, Boëlle P-Y, Muresan I-P, Alamowitch S. Strokes in Sneddon syndrome without antiphospholipid antibodies. *Ann Neurol*. 2015;77(5):817-829. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84928215095&doi=10.1002%2Fana.24382&rtnerID=40&d5=ee542352ecc1b1b486f6a8432b969e0c
14. Starmans NLP, van Dijk MR, Kappelle LJ, Frijns CJM. Sneddon syndrome: a comprehensive clinical review of 53 patients. *J Neurol*. 2021;268(7):2450-2457.
15. Rodríguez-Pazos L, Gómez-Bernal S, Sánchez-Aguilar D, Rodríguez-Granados MT, Toribio J. Sneddon syndrome associated with urticarial vasculitis and factor V leiden mutation. *Actas Dermosifiliogr*. 2010;101(6):569-571. https://linkinghub.elsevier.com/retrieve/pii/S1578219010708520
16. Samanta D, Cobb S, Arya K. Sneddon syndrome: a comprehensive overview. *J Stroke Cerebrovasc Dis*. 2019;28(8):2098-2108.
17. Yilmaz E, Arsava EM, Gocmen R, Oguz KK, Arat A, Topcuoglu MA. Characteristic imaging features of neurovascular involvement in primary Sneddon's syndrome: an analysis of 12 cases. *Neurol Sci*. 2021;42(6):2363-2369. https://link.springer.com/10.1007/s10072-020-04621-0
18. Zelger B, Sepp N, Stockhammer G, et al. Sneddon's syndrome: a long-term follow-up of 21 patients. *Arch Dermatol*. 1993;129(4):437-447. doi:10.1001/archderm.1993.01680250049006
19. Bottin L, Francès C, De Zuttere D, Boëlle PY, Muresan IP, Alamowitch S. Strokes in Sneddon syndrome without antiphospholipid antibodies. *Ann Neurol*. 2015;77(5):817-829. https://onlinelibrary.wiley.com/doi/full/10.1002/ana.24382
20. Bayrakli F, Erkek E, Kurtuncu M, Ozgen S. Intraventricular hemorrhage as an unusual presenting form of Sneddon syndrome. *World Neurosurg*. 2010;73(4):411-413. https://www.scopus.com/inward/record.uri?eid=2-s2.0-77955868171&doi=10.1016%2Fj.wneu.2010.01.010&rtnerID=40&d5=110aead5ba93122636f54e14e36c7062
21. Kabak E, Clusmann J, Abu Jhaisha S, et al. An unusual case of intracerebral hemorrhage: exploring the link with Sneddon's syndrome. *Med Klin Intensivmed Notfallmed*. 2024;119(1):66-68.
22. Killeen T, Wanke I, Mangiardi J, Cesnulis E. Ruptured, fusiform, distal lenticulostriate aneurysm causing intraventricular haemorrhage in a patient with antiphospholipid-negative Sneddon's syndrome. *Clin Neurol Neurosurg*. 2014;116:80-82.
23. Boesch SM, Plörer AL, Auer AJ, et al. The natural course of Sneddon syndrome: clinical and magnetic resonance imaging findings in a prospective six year observation study. *J Neurol Neurosurg Psychiatry*. 2003;74(4):542-544. https://jnnp.bmj.com/lookup/doi/10.1136/jnnp.74.4.542
24. Tietjen GE, Al-Qasmi MM, Gunda P, Herial NA. Sneddon's syndrome: another migraine-stroke association? *Cephalalgia*. 2006;26(3):225-232.
25. Tietjen GE, Al-Qasmi MM, Shukairy MS. Livedo reticularis and migraine: a marker for stroke risk? *Headache*. 2002;42(5):352-355.
26. Cavestro C, Richetta L, Pedemonte E, Asteggiano G. Sneddon's syndrome presenting with severe disabling bilateral headache. *J Headache Pain*. 2009;10(3):211-213. https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1007/s10194-009-0109-3
27. Fabiani G, Filho RM, Koppe GL, Demartini Z, Gatto LAM. Cognitive and psychiatric changes as first clinical presentation in sneddon syndrome. *Dement e Neuropsychol*. 2018;12(2):216-219. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85048751678&doi=10.1590%2F1980-57642018dn12-020016&partnerID=40&md5=a40eed2c013354be8fe6cd8fce1915f3
28. Karoui M, Baklouti E, Ben Mohamed D, Riahi H, Chelli-Bouaziz M. Cognitive and psychiatric signs revealing Sneddon syndrome: a case report. *Clin Case Rep*. 2023;11(10):e8013.
29. Hsu F-F, Chung K-H. Psychosis with suicide attempt in Sneddon syndrome. *Psychiatr Clin Neurosci*. 2017;71:147-148.
30. Quenardelle V, Willaume T, Benoilid A, Collongues N, De Seze J. [A first seizure revealing Sneddon's syndrome]. *Rev Neurol (Paris)*. 2014;170(1):55-57. https://linkinghub.elsevier.com/retrieve/pii/S0035378713010059
31. Sajjan V, Lunge S, Swamy M, Pandit A. Livedo reticularis: a review of the literature. *Indian Dermatol Online J*. 2015;6(5):315-321. https://journals.lww.com/10.4103/2229-5178.164493
32. Madani A, Almutairi HM, Alshathry YH, Albinhar T, Barakeh MM. Sneddon syndrome: a case report from Saudi Arabia. *Cureus*. 2024;16:e55509.
33. Schlez A, Lischka G, Schaumburg-Lever G, Ganten T, Jünger M. Raynaud symptoms as principal signs in a case of Sneddon's syndrome. *J Eur Acad Dermatol Venereol*. 2001;15(4):365-366. doi:10.1046/j.0926-9959.2001.00276-7.x
34. Hj G. M. L. Angiomatosis associated with Sneddon's syndrome. *N Engl J Med*. 2024;350(12):e11. doi:10.1056/ENEJMicm020035
35. Song HB, Woo SJ, Jung CK, et al. Acute central retinal artery occlusion associated with livedoid vasculopathy: a variant of Sneddon's syndrome. *Kor J Ophthalmol*. 2013;27(5):376-380. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84901874295&doi=10.3341%2Fkjo.2013.27.5.376&rtnerID=40&d5=9e8b7bbe0407c1f73d1acd763708c7e9
36. Song HB, Woo SJ. Author reply: central retinal artery occlusion in a young female: Sneddon's syndrome versus Susac syndrome? *Kor J Ophthalmol*. 2014;28:113-114.
37. Jonas J, Kölble K, Völcker HE, Kalden JR. Central retinal artery occlusion in Sneddon's disease associated with antiphospholipid antibodies. *Am J Ophthalmol*. 1986;102(1):37-40.
38. Aggermann T, Haas P, Binder S. Central retinal vein occlusion as a possible presenting manifestation of Sneddon syndrome. *J Neuro Ophthalmol*. 2007;27:240-241.
39. Jiménez-Gallo D, Albarrán-Planelles C, Linares-Barrios M, González-Fernández JA, Espinosa-Rosso R, Báez-Perea JM. Sneddon syndrome presenting with unilateral third cranial nerve palsy. *J Neuro Ophthalmol*. 2014;34(1):50-52. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84896696127&doi=10.1097%2FWNO.0b013e3182a3060d&rtnerID=40&d5=86c2a5c7ad3bb4a4acde12cbd256253b
40. Narbay G. Sneddon's syndrome in a patient with homonymous hemianopia with macular sparing. *Bull Soc Belge Ophtalmol*. 1996;263:103-107.
41. Kriet M, Fiqhi A, Bouya Y, Louaya S, Laktaoui A. [Sneddon syndrome and antiphospholipid antibodyies: an etiology of later al homonymous hemianopia]. *Bull Soc Belge Ophtalmol*. 2010;316:43-47.

42. Rehany U, Kassif Y, Rumelt S. Sneddon's syndrome: neuro-ophthalmologic manifestations in a possible autosomal recessive pattern. *Neurology*. 1998;51(4):1185-1187. https://www.neurology.org/doi/10.1212/WNL.51.4.1185
43. Nagai N, Ohta Y, Izumi-Nagai K, Shinoda H, Tsubota K, Ozawa Y. Sneddon's syndrome with optic disc macroaneurysm and macular edema successfully treated with subtenon steroid injection. *Acta Ophthalmol*. 2016;94(6):e517-e519. https://onlinelibrary.wiley.com/doi/10.1111/aos.12909
44. Gobert A. Sneddon's syndrome with bilateral peripheral retinal neovascularization. *Bull Soc Belge Ophtalmol*. 1995;255:85-90.
45. Romera Romero P, Monés Llivina A, Blazquez Abisu A, Sabala Llopart A. Infarto de nervio óptico asociado a síndrome de Sneddon. *Arch Soc Esp Oftalmol*. 2015;90(4):180-184. https://linkinghub.elsevier.com/retrieve/pii/S0365669114002706
46. Fiore A, Ternacle J, Piscitelli M, Fardet L, Mongardon N. Sneddon syndrome: anesthetic and surgical challenges in cardiac valve surgery. *Perfusion*. 2020;35(7):710-711. https://journals.sagepub.com/doi/10.1177/0267659119899333
47. Diosteanu R, Schuler G, Müller U. Cardiac valve degeneration in a patient with Sneddon syndrome. *Clin Res Cardiol*. 2015;104(6):453-455. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84929959078&doi=10.1007%2Fs00392-014-0802-3&rtnerID=40&d5=8c5ebac6850c28b001daebc5c0a84558
48. Scheuermann S, Schlundt C. STEMI of the anterior wall associated with Sneddon's syndrome. *Herz*. 2014;39(3):352-353.
49. Nassenstein K, Breuckmann F, Dissemond J, Barkhausen J. Sneddon's syndrome: cardiac involvement detected by magnetic resonance imaging. *Heart*. 2006;92(11):1660. https://heart.bmj.com/lookup/doi/10.1136/hrt.2006.092999
50. Dominguez F, Pieske B, Kelle S. Cardiac manifestations of Sneddon's syndrome. *Int J Cardiol*. 2015;190:275-276. https://linkinghub.elsevier.com/retrieve/pii/S016752731500889X
51. Giovachini L, Pham V, Picard F, Fischer Q. Obstructive valve thrombosis after transcatheter aortic valve replacement (TAVR) in Sneddon syndrome without antiphospholipid antibodies. *BMJ Case Rep*. 2023;16(6):e254309. https://casereports.bmj.com/lookup/doi/10.1136/bcr-2022-254309
52. Zelger B, Sepp N, Stockhammer G, et al. Sneddon's syndrome. A long-term follow-up of 21 patients. *Arch Dermatol*. 1993;129(4):437-447. doi:10.1001/archderm.1993.01680250049006
53. Khoo LA, Belli AM. Superior mesenteric artery stenting for mesenteric ischemia in Sneddon's syndrome. *Br J Radiol*. 1999;72(858):607-609. doi:10.1259/bjr.72.858.10560345
54. Heng Y, Tang Y-F, Zhang X-W, Duan J-F, Shi J, Luo Q. Sneddon's syndrome concurrent with cerebral venous sinus thrombosis: a case report. *World J Clin Cases*. 2023;11(31):7656-7662. https://www.wjgnet.com/2307-8960/full/v11/i31/7656.htm
55. Kirsanova TV, Kozlovskaia NL, Kalashnikova LA, Smirnova TV, Roshchupkina SV, Khafizova EI. [Characteristics of the kidney lesion in a patient with Sneddon's syndrome]. *Ter Arkh*. 2009;81(8):73-77. https://www.ncbi.nlm.nih.gov/pubmed/19799206
56. Hernández García E, Torres Sánchez MJ. Renal involvement in Sneddon syndrome. *Nefrologia. Spain*. 2021;41:81-82.
57. Dutra LA, Braga-Neto P, Pedroso JL, Barsottini OGP. Sneddon's syndrome: case report and review of its relationship with antiphospholipid syndrome. *Einstein (São Paulo)*. 2012;10(2):230-232. https://www.scielo.br/scielo.php?script=sci_arttext&id=S1679-45082012000200018&lng=en&tlng=en
58. Yilmaz E, Arsava EM, Gocmen R, Oguz KK, Arat A, Topcuoglu MA. Characteristic imaging features of neurovascular involvement in primary Sneddon's syndrome: an analysis of 12 cases. *Neurol Sci*. 2021;42(6):2363-2369. https://www.scopus.com/inward/record.uri?eid=2-s2.0-85092386859&doi=10.1007%2Fs10072-020-04621-0&rtnerID=40&d5=ee84872dd8e6f4865004c7de566b8da7
59. Collantes-Rodríguez C, Jiménez-Gallo D, Arjona-Aguilera C, Ossorio-García L, Linares-Barrios M. Treatment of skin ulcers secondary to sneddon syndrome with alprostadil (prostaglandin E1). *JAMA Dermatol*. 2016;152(6):726-727.
60. Ekker MS, Verhoeven JI, Schellekens MMI, et al. Risk factors and causes of ischemic stroke in 1322 young adults. *Stroke*. 2023;54(2):439-447. doi:10.1161/STROKEAHA.122.040524
61. Anna B, Michela M, Elisa C, et al. The diagnostic challenge of Divry van Bogaert and Sneddon Syndrome: report of three cases and literature review. *J Neurol Sci*. 2016;364:77-83. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84961207216&doi=10.1016%2Fj.jns.2016.03.011&rtnerID=40&d5=761062d5bf063c6e6b2fe1c337d92e0c
62. Stockhammer G, Felber SR, Zelger B, et al. Sneddon's syndrome: diagnosis by skin biopsy and MRI in 17 patients. *Stroke*. 1993;24(5):685-690. doi:10.1161/01.STR.24.5.685
63. Starmans NLP, Zoetemeyer S, van Dijk MR, Kappelle LJ, Frijns CJM. The diagnostic value of skin biopsies in Sneddon syndrome. *PLoS One*. 2021;16:e0253365. https://dx.plos.org/10.1371/journal.pone.0253365
64. Capecchi M, Abbattista M, Ciavarella A, Uhr M, Novembrino C, Martinelli I. Anticoagulant therapy in patients with antiphospholipid syndrome. *J Clin Med*. 2022;11:6984.
65. Sun JZ, Zhang FH, Gao F, Wang JH, Selim M, Lou M. Intravenous thrombolysis in Sneddon's syndrome. *J Clin Neurosci*. 2012;19(2):326-328. https://www.scopus.com/inward/record.uri?eid=2-s2.0-84856212482&doi=10.1016%2Fj.jocn.2011.05.024&rtnerID=40&d5=3b7456ddb0e27eec6a04d8f8fa212442
66. Narwutsch A, Wohlrab J, Sperfeld A-D, Sunderkötter C. Combination therapy for Sneddon syndrome to reduce the incidence of cerebrovascular complications. *J der Dtsch Dermatologischen Gesellschaft = J Ger Soc Dermatology JDDG*. 2024;22(7):947-954.
67. Flöel A, Imai T, Lohmann H, Bethke F, Sunderkötter C, Droste DW. Therapy of Sneddon syndrome. *Eur Neurol*. 2002;48(3):126-132.
68. Hannon PM, Kuo S-HH, Strutt AM, York MK, Kass JS. Improvement of neurological symptoms and memory and emotional status in a case of seronegative Sneddon syndrome with cyclophosphamide. *Clin Neurol Neurosurg*. 2010;112(6):544-547. https://www.scopus.com/inward/record.uri?eid=2-s2.0-77952885934&doi=10.1016%2Fj.clineuro.2010.04.002&rtnerID=40&d5=3166a54886581f296151013b9ef83afa
69. Barnini T, Silvestri E, Emmi G, D'Elios MM, Emmi L. Digital ulcers secondary to Sneddon's syndrome successfully treated with Bosentan: not only useful in systemic sclerosis. *Auto Immun Highlights*. 2013;4(2):67-68. https://autoimmunhighlights.biomedcentral.com/articles/10.1007/s13317-012-0037-0
70. Seok HH, Noh Y, Jeong EC, Park JU, Hong YH. Treatment of refractory lower extremity ulcer associated with Sneddon's syndrome. *Arch Plast Surg*. 2013;40(3):277-280. https://www.thieme-connect.de/DOI/DOI?10.5999/aps.2013.40.3.277
71. Fetoni V, Grisoli M, Salmaggi A, Carriero R, Girotti F. Clinical and neuroradiological aspects of Sneddon's syndrome and primary antiphospholipid antibody syndrome. A follow-up study. *Neurol Sci*. 2000;21:157-164.