Sneddon Syndrome: Can it be a Cause of Medically Resistant Headache?: Case Report

Sneddon Sendromu: Tedaviye Dirençli Baş Ağrısının Nedeni Olabilir mi?

Aysel MİLANLIOĞLU,[a]
Ayşe Serap KARADAĞ,[b]
Alper GÖKGÜL,[a]
Serap GÜNEŞ BİLGİLİ,[b]
Temel TOMBUL[a]

Departments of
[a]Neurology,
[b]Dermatology,
Yüzüncü Yıl University
Faculty of Medicine, Van

Geliş Tarihi/*Received:* 28.02.2013
Kabul Tarihi/*Accepted:* 23.04.2013

The case report was presented as a poster at 48th National Neurology Congress, 16-22 November 2012, Antalya

Yazışma Adresi/*Correspondence:*
Aysel MİLANLIOĞLU
Yüzüncü Yıl University
Faculty of Medicine,
Department of Neurology, Van,
TÜRKİYE/TURKEY
ayselmilanlioglu@yahoo.com

ABSTRACT Sneddon syndrome is a rarely seen, progressive, non-inflammatory thrombotic vasculopathy. It induces an excessive endothelial proliferation leading to occlusion of small and medium sized vessels, particularly in the brain and skin and is characterized by triad of cerebrovascular attacks, benign type hypertension and livedo reticularis. The common presentations of this disease include vascular dementia, cardiac valvulopathies, renal failure, hypertension, seizure, peripheral nerve involvement, venous sinus thrombosis, and headache. In the nervous system involvement, headache is seen 85% of patients and usually indicator of increased stroke risk. In the case report, we present 27 year-old female who has medically refractory headache in consequence of Sneddon syndrome and treated successfully with acetylsalicylic acid and pentoxifylline.

Key Words: Sneddon syndrome; headache; pentoxifylline; central nervous system diseases

ÖZET Sneddon sendromu nadir görülen, ilerleyici, non-inflamatuvar, trombotik bir vaskülopatidir. Sendrom aşırı endotelyal proliferasyon ile özellikle beyin ve derideki küçük ve orta çaplı damarlarda oklüzyona neden olmakta ve serebrovasküler ataklar, benign tip hipertansiyon ve livedo retikularis triyadı ile karakterize olduğu görülmektedir. Hastalığın sık görülen klinik prezentasyonları vasküler demans, kardiyak valvülopatiler, böbrek yetmezliği, hipertansiyon, epileptik nöbet, periferik sinir tutulumu, venöz sinüs trombozu, ve baş ağrısıdır. Santral sinir sistemi tutulumu olarak baş ağrısı hastaların %85'de görülmekte olup, genellikle artmış inme riskinin bir göstergesidir. Bu olgu raporunda biz, Sneddon sendromuna bağlı tedaviye dirençli baş ağrısı olan, asetilsalisilik-asit ve pentoksifilin ile başarılı bir şekilde tedavi edilen 27 yaşındaki kadın hastayı sunuyoruz.

Anahtar Kelimeler: Sneddon sendromu; baş ağrısı; pentoksifilin; santral sinir sistemi hastalıkları

Turkiye Klinikleri J Neur 2013;8(3):119-22

Sneddon syndrome (SS) is a rarely seen and progressive non-inflammatory thrombotic vasculopathy. It induces an excessive endothelial proliferation leading to occlusion of small and medium sized vessels, particularly in the brain and skin.[1]

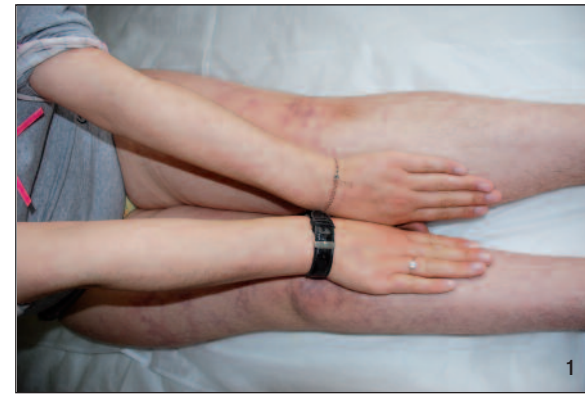
Sneddon syndrome was first described by English dermatologist Sneddon in 1965. It is characterized by triad of cerebrovascular attacks (that is usually mild and presents with mild residual defects), benign type hypertension and livedo reticularis.[2] The two main features are livedo reticularis and lacunar subcortical infarcts. The other common presentations include vascular dementia, cardiac valvulopathies, renal failure, hypertension, seizure, peripheral nerve involvement, venous sinus thrombosis, and headache.[3]

A 27 year-old female admitted to our clinic for medically refractory headache was diagnosed as SS. Herein, we presented the case due to its rarity and its responsiveness to the treatment.

CASE REPORT

A 27 year-old female came to our clinic for medically refractory headache for one and half year. The headache started from the back of the head that spreading to the anterior part of the head. It was throbbing headache and not associated with nausea, photophobia or phonophobia. The duration of headache ranged from several hours to few days. She developed violescent skin lesions for 2 years. She was previously diagnosed with possible pseudotumor cerebri and was treated with acetazolamide 750 mg three times a day that was not beneficial. She had residual right leg weakness due to polio sequela. The past medical history was negative for epilepsy, and recurrent abortion or miscarriage. Blood pressure was 140/90 mmHg, and heart rate was 80/min and rhythmic. Dermatological examination revealed erythematous, violaceous lesions with irregular borders and livedoid appearance that was widespread distribution, particularly on legs, arms, trunk and thigs (Figures 1, 2). Raynaud's phenomenon was positive. Other systems including neurological examination were unremarkable. Funduscopic examination and visual field test were within normal limits. Lumbar puncture was repeated since she was diagnosed with possible pseudotumor cerebri. However, the opening pressure was 10 cm-H2O and the biochemical and microbiological analysis of cerebrospinal fluid was normal. The possibility of pseudotumor cerebri was excluded due to normal opening pressure. A cranial magnetic resonance imaging showed milimetric hyperintense lesions on the periventricular white matter on T2-Flair sequences. The carotid and vertebral arteries color doppler and cerebral venography were within normal limits. Biopsy was performed on the skin lesion. The histopathological examination showed livedo reticularis.

Laboratory investigation including complete cell count, urinalysis, comprehensive metabolic panel, protein electrophoresis, C-reactive protein, rheumatoid factor, erythrocyte sedimentation rate were normal.



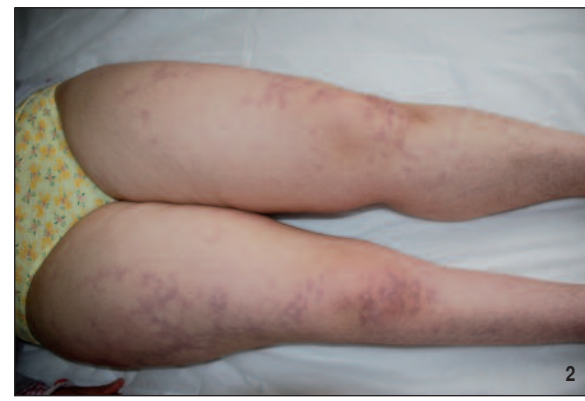


FIGURE 1,2: Erythematous, violaceous, reticular lesions are seen particularly on the arms, legs, truck and thigs.

Anti-nuclear antibody, anti-dsDNA, lupus anticoagulants, anti-cardiolipin, IgG and IgM antibodies, anti-neutrophil cytoplasmic antibody, anti-gliadin, anti-centromer, and anti-ribonucleoprotein antibodies were negative as well.

The coagulation panel including prothrombin time, international normalized ratio, protein C and S, anti-thrombin 3 activities, and active protein C resistant showed low protein S level (42%, normal range 60%-140%). Syphilis, hepatitis B ve C serology were negative.

A transthoracic echocardiogram showed moderate to severe degree of mitral valve insufficiency.

Based on the clinical and diagnostic findings, she was diagnosed with SS and treated with acetylsalicylic acid 300 mg once daily, and pentoxifylline 400 mg two times daily. The headache was dra-

matically reduced within 3 days and completely resolved during 1-month follow up.

DISCUSSION

Sneddon syndrome is characterized by ischemic cerebrovascular episodes and generalized livedoid skin eruptions. The coincidence was first described by Champion and Rook in 1960 but the relationship was first illustrated by Sneddon in 1965.[2,4] SS is frequently seen in female (age range 20-42 years). The annual incidence was 4/1.000.000. The mortality rate is 9.5% during average 6.2 years follow up period. The etiopathogenesis is still unclear. However, central nervous system and skin findings are related to focal thrombotic and embolic events. Up to now, autosomal dominant and recessive cases have been reported, but the gene locus is still unknown.[5] There was no family history in our case.

Subclinical systemic involvement including ocular, peripheral nervous, gastrointestinal, renal and cardiac system was seen 50-70% of the patients.[6] The cardiac involvement can be ischemic and valvular involvement (the most common valve is mitral valve). Mild or moderate hypertension is seen in 60-80% of the cases.[7] In our case, mild hypertension and moderate to severe mitral valve regurgitation were recorded.

Nervous system involvements include venous thrombosis, epilepsy, vascular dementia, transient ischemic attack, hemiplegia, hemihypoesthesia, hemianopsia, tremor, chorea, myelopathy, encephalopathy, and secondary headache.[8] Headache secondary to central nervous system involvement is seen around 85% of the patients, usually medically refractory headache and indicator of increased stroke risk.

Livedo reticularis is an important diagnostic clue that is helpful for the diagnosis. The histopathological finding of livedo reticularis is non-inflammatory arteriopathy of the small and medium sized vessels. The skin biopsy can be negative or non-specific that is related to biopsy site. The biopsy taken from central lesions shows more positive results than from peripheral lesions. The digital artery biopsy of seven patients with negative skin biopsy showed intimal hyperplasia, luminal narrowing, degeneration or reduplication of internal elastic lamina, and adventitial fibrosis.[9] In our case, the skin biopsy findings showed livedo reticularis which is non-specific.

Investigation including antiphospholipid antibody, anti-nuclear antibody, anti-dsDNA, lupus anticoagulants, beta 2 glycoprotein, protein C, protein S, and anti-thrombin 3 should be performed for the diagnosis of SS. Antiphospholipid antibody is positive in 80% of the patients. Protein S deficiency is rarely detected in patients with SS.[8] In our case, the protein S level was low, and the other tests including antiphospholipid antibody were unremarkable.

There is no available treatment for SS. Several medications including corticosteroids, immunomodulators, beta-adrenergic blockers have been tried, however were not efficient. Nifedipine can be effective in treatment of livedo reticularis and acrocyanosis, but not effective in prevention of cerebrovascular disease.[10]

Patients with SS can develop medically refractory headache.[1] Although definite treatment has not been described, antiplatelet and anticoagulation treatments can be effective by decreasing the blood viscosity.[11] We administered acetylsalicylic acid 300mg daily and pentoxifylline 400 mg twice daily. Headache was dramatically reduced on the 3rd day of the treatment. The patient was satisfied with the result of the treatments on the one-month follow up.

In conclusion, SS is a serious systemic disease that can cause morbidity and mortality. Even though no definitive treatment for medically refractory headache, antiplatelet and peripheral vasodilator agents can be beneficial. Further clinical trials with large number of patients are warranted on the effectiveness of antiplatelet and anticoagulation treatments.

REFERENCES

1. Cavestro C, Richetta L, Pedemonte E, Asteggiano G. Sneddon's syndrome presenting with severe disabling bilateral headache. J Headache Pain 2009;10(3):211-3.
2. Sneddon IB. [Cerebro-vascular lesions and livedo reticularis]. Br J Dermatol 1965;77:180-5.
3. Bolayir E, Yilmaz A, Kugu N, Erdogan H, Akyol M, Akyuz A. Sneddon's syndrome: clinical and laboratory analysis of 10 cases. Acta Med Okayama 2004;58(2):59-65.
4. Champion RH, Rook A. [Livedo reticularis]. Proc R Soc Med 1960;53:961-2.
5. Bayrakli F, Erkek E, Kurtuncu M, Ozgen S. Intraventricular hemorrhage as an unusual presenting form of Sneddon syndrome. World Neurosurg 2010;73(4):411-3.
6. Wohlrab J, Francès C, Sullivan KE. Strange symptoms in Sneddon's syndrome. Clin Immunol 2006;119(1):13-5.
7. Legierse CM, Canninga-Van Dijk MR, Bruijnzeel-Koomen CA, Kuck-Koot VC. Sneddon syndrome and the diagnostic value of skin biopsies - three young patients with intracerebral lesions and livedo racemosa. Eur J Dermatol 2008;18(3):322-8.
8. Sayin R, Bilgili SG, Karadag AS, Tombul T. Sneddon syndrome associated with Protein S deficiency. Indian J Dermatol Venereol Leprol 2012;78(3):407.
9. Stockhammer G, Felber SR, Zelger B, Sepp N, Birbamer GG, Fritsch PO, et al. Sneddon's syndrome: diagnosis by skin biopsy and MRI in 17 patients. Stroke 1993;24(5):685-90.
10. Geschwind DH, FitzPatrick M, Mischel PS, Cummings JL. Sneddon's syndrome is a thrombotic vasculopathy: neuropathologic and neuroradiologic evidence. Neurology 1995;45 (3 Pt 1):557-60.
11. Martinelli A, Martinelli P, Ippoliti M, Giuliani S, Coccagna G. Sneddon syndrome presenting with hemicranic attacks: a case report. Acta Neurol Scand 1991;83(3):201-3.