Sjögren’s Syndrome Presenting as Ischemic Stroke

M. Bragoni, MD; V. Di Piero, PhD; R. Priori, MD; G. Valesini, MD; G.L. Lenzi, MD

Background We describe a young woman who presented with minor stroke as a first clinical symptom of Sjögren’s syndrome (SS) in the absence of well-known risk factors for cerebrovascular disease.

Case Description The medical history included recurrent miscarriages and sun rashes, which directed the diagnosis toward immunologic disorders such as systemic lupus erythematosus and antiphospholipid antibody syndrome, which are often associated with stroke. Only complete laboratory testing, including SSB antibody studies, and ophthalmologic and salivary gland evaluation revealed the correct diagnosis.

Conclusions Sjögren’s syndrome should be considered among the causes of stroke, especially in a young female patient. (Stroke. 1994;25:2276-2279.)

Key Words • risk factors • Sjögren’s syndrome • young adults • cerebrovascular disorders

Sjögren’s syndrome (SS) is an autoimmune disease characterized by focal or confluent lymphocytic infiltrates in the exocrine glands; the main clinical symptoms are dry eyes and xerostomia. Females are affected more frequently than males.

The psychiatric and neurological complications of SS have been described. Peripheral nervous system (PNS) complications are more common than central nervous system (CNS) complications. CNS complications occur in approximately 25% of patients, usually late in the course of the disease. Few patients have been described with CNS or PNS symptoms as the first clinical presentation of SS, but an embolic stroke associated with cardiomyopathy has been described as the first clinical presentation.

We describe a patient with minor stroke as the presenting feature of SS; no other risk factors for stroke were identified.

Case Report

A 44-year-old woman was admitted to our unit with mild weakness of the right arm, concentration and memory difficulties, and a recent onset of xerostomia. Four months earlier she had presented with a sudden onset of confusion, speech problems, weakness, and sensory loss of the right arm. The confusion subsided in a few hours, and the other symptoms subsided within 48 hours. At that time a computed tomographic scan of the brain, a carotid ultrasound, and cerebral angiography were normal. A transient ischemic attack was diagnosed at that time.

Her medical history included three miscarriages, headaches, a facial rash when exposed to the sun, and arthralgia for several years. No other risk factors such as hypertension, diabetes, smoking, contraceptive drug use, or family or personal history of thromboses were present.

The physical general examination revealed patches of skin depigmentation in both arms, a small thyroid nodule, and a cardiac systolic murmur. The neurological examination was normal except for weakness, hyperreflexia, and hypoesthesia of the right arm. An extensive neuropsychological assessment revealed mild impairment in regard to attention and visuospatial problems, long-term verbal memory deficits, and word-finding problems.

Routine laboratory tests were all normal except for erythrocyte sedimentation rate (15; normal, <10), hypergammaglobulinemia (25%; normal, 12% to 20%), slight serum IgG increase (1430 mg/dL; normal range, 700 to 1350 mg/dL), and hypocholesterolemia (130 mg/dL; normal range, 160 to 240 mg/dL).

Other laboratory testing revealed the presence of antinuclear antibodies, as shown by indirect immunofluorescence on human epithelial cells (pattern coarse speckled, standard serum dilution 1/40) and anti-SSB antibodies (counterimmunoelectrophoresis and Western blotting). Anti-DNA antibodies and other anti-extractable nuclear antigens (anti-SSA, anti-Smith, anti-scleroderma 70), lupus anticoagulant, anticoagulant, anticardiolipin antibodies, rheumatoid factor, cryoglobulins, and circulating immune complexes were negative. A platelet aggregation study and fibrinogen level were normal. The plasma levels of inhibitory coagulation factor proteins such as antithrombin III, protein C, and protein S were normal.

A standard electrocardiogram and 24-hour Holter electrocardiogram were normal. Transthoracic and transesophageal echocardiography revealed thickening of the mitral valve associated with a mild tricuspid insufficiency. Somatosensory evoked potentials, brain stem auditory evoked potentials, electroencephalogram, and nerve conduction velocities were in the normal range. A brain computed tomographic scan was normal; however, magnetic resonance imaging (MRI)
Magnetic resonance images show two areas of hyperintensity on $T_2$-weighted image (right panel) and corresponding hypointensity on $T_1$-weighted image (left panel) in the territory of the left middle cerebral artery, involving the cortex of the insula and the globus pallidum. $R$ indicates right; $L$, left.

showed two areas of hyperintensity on $T_2$-weighted images and corresponding hypointensity on $T_1$-weighted images in the territory of the left middle cerebral artery, involving the cortex of the insula and the globus pallidum (Figure).

An ophthalmologic examination revealed an abnormal break time and a rose bengal score greater than 4, diagnostic of keratoconjunctivitis sicca. Minor salivary gland biopsy revealed more than one focus of lymphocytes in 4 mm$^2$ of tissue, thus determining a grade IV lymphocytic adenitis according to the Chishol-Mason scale and confirming the diagnosis of SS.

The patient was treated with steroid and immunosuppressive therapy (dexamethasone, 20 mg once a week, and methotrexate, 7.5 mg once a week). In the following months she also presented with an autoimmune thyroiditis, which improved after adequate therapy. We continued to follow up the patient for more than 2 years, and she did not present with any other cerebral ischemic symptoms.

Discussion

In this patient the onset and time course of the neurological symptoms as well as the MRI findings suggest the occurrence of a minor stroke in the vascular territory of the left middle cerebral artery.

Normal carotid duplex scan and cerebral angiography ruled out disease of the extracranial and intracranial large arteries as a possible cause of stroke. A possible cardioembolic mechanism was considered, but transthoracic and transesophageal echocardiography ruled out the presence of relevant cardiac and aortic abnormalities. The only detectable cardiac abnormality was thickening of the mitral valves, which is not in itself considered an independent risk factor for cardiac embolism to the brain. Additionally, Hess found that only the combination of antiphospholipid antibodies and mitral valve abnormalities was associated with brain embolism. In our patient antiphospholipid antibodies were negative on more than one occasion. Finally, we did not find any detectable cardiac arrhythmias.

Because of her young age and the absence of vascular and cardiac risk factors for cerebrovascular disease, hematologic and immunologic abnormalities were considered in the etiopathogenesis of the stroke. A congenital or acquired deficiency of inhibitory coagulation factor proteins such as antithrombin III, protein C, and protein S, which has been established as probable cause of ischemic stroke in both young and old patients, was ruled out. Possible immunologic abnormalities were then considered. The clinical clues that alerted us to the presence of an underlying immunologic disorder were the presence of three miscarriages and sun rashes in her medical history. The possibilities of antiphospholipid antibody syndrome and systemic lupus erythematosus, often associated with stroke, were considered. Our patient did not fulfill established criteria for systemic lupus erythematosus or for antiphospholipid antibody syndrome. On the other hand, the presence of antinuclear antibodies and anti-SSB antibodies, a specific marker for SS, led us to perform more thorough testing for SS. The ophthalmologic testing and the salivary gland biopsy confirmed the diagnosis of SS, according to the criteria of the most recent classification of SS. Moreover, the association with autoimmune thyroiditis and vitiligo frequently described in SS, a
well-known polyglandular (exocrine and endocrine) autoimmune disease, completed the clinical presentation in our patient.

Approximately 25% of SS patients present with CNS complications and approximately 10% to 20% with PNS complications. The entire neuroaxis, the peripheral and cranial nerves, and the ganglia may be involved during SS. A neuropsychological presentation of SS is considered unusual in either the PNS or the CNS. A stroke as first clinical presentation of SS has been described in association with cardiomyopathy, but this was not true in our case. This is the first well-documented large-artery minor stroke occurring in a young woman in whom no cause other than uncomplicated SS has been found.

The etiopathogenesis of the neurological damage in SS seems to be immunologically mediated. The most common mechanism of PNS and CNS involvement during SS is due to vasculitis of small vessels. Necrotizing vasculitis involving the entire neuropathosis has been described in two autopsy cases of SS. T- and B-lymphocytic perivascular leptomeningeal and intraparenchymal infiltration is described in a brain biopsy in a case of reversible dementia associated with SS. A vasculorum vasculitis with monocytes, lymphocytes, and neutrophils has been described in association with clinical symptoms of polyneuropathy in SS patients. Antinuclear autoantibodies have also been described for PNS complications during SS. On the other hand, Grauss et al did not find signs of vasculitis or autoantibodies against myelin in patients affected by sensory neuropathy, suggesting another possible cell-mediated mechanism.

According to Alexander, brain autopsies in SS patients who died in association with severe CNS complications showed minute microhemorrhages and/or microinfarcts associated with extensive small parenchymal endothelial damage secondary to a few mononuclear perivascular inflammations. According to the author, this type of vasculopathy would be progressive and cause clinical symptomatology only when larger lesions involve a clinically critical region of the brain.

No more than 20% of patients affected by SS have abnormal cerebral angiography suggestive of brain vasculitis. In our patient normal cerebral angiography ruled out the presence of extracranial and intracranial arterial diseases but gave us limited information about possible small-vessel disease. Brain biopsy, potentially diagnostic for inflammatory disease or small-vessel vasculitis, was refused by the patient.

CNS involvement during SS may be studied noninvasively with MRI. This seems to be the most sensitive among the noninvasive tests for SS, being able to detect lesions in more than 75% of patients, whereas computed tomographic scan of the brain is positive in only 20% of patients. MRI abnormalities may include areas of increased signal intensity on T2-weighted images and decreased signal intensity on the corresponding T1-weighted images. The lesions may be located in the periventricular deep white matter and less frequently in the gray matter. In our patient the involvement of the gray matter of insula and globus pallidum was demonstrated by the MRI.

In our patient the stroke represented the clinical onset of SS. Only a thorough exclusion of other common causes of stroke and a complete hematologic and immunologic screening for disorders rarely associated with cerebral vessel disease revealed the diagnosis.

In conclusion, we believe that young stroke patients without well-known risk factors for stroke should also be evaluated for SS, even in the absence of other clinical symptomatology. The laboratory screening should include immunologic tests such as antinuclear antibodies and anti-SSB and/or anti-SSA antibodies; ophthalmologic and salivary gland evaluation should be performed only if the immunologic screening for SS is positive.

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References


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