Familial Sneddon’s syndrome

Abstract We report the familial occurrence and apparent autosomal dominant inheritance of Sneddon’s syndrome with variable clinical expression. The proband, a 40-year-old woman, presented with livedo reticularis and progressive neurological deterioration following a stroke. The diagnosis was confirmed by cerebral angiogram and skin biopsy, both showing the characteristic findings. Two of the patient’s sisters were reported to have been similarly affected in the past. Her mother, two additional siblings and five of her seven children exhibited various vasospastic skin phenomena. Familial aggregation of this disorder may be common and a genetic basis may be involved in its pathogenesis.

Key words Sneddon’s syndrome • Livedo reticularis • Antiphospholipid antibodies • Genetic cerebrovascular disorder

Introduction

Sneddon’s syndrome (SS) refers to widespread irregular livedo reticularis (LR, livedo racemosa) of a fixed nature accompanied by a progressive ischaemic cerebrovascular involvement [30]. Occlusion of small- to medium-sized arteries of undetermined aetiology underlies the neurocutaneous manifestations and leads to permanent disability [29]. The disorder has been described in more than 120 patients; it affects predominantly 30- to 50-year-old women and is generally considered sporadic [30], although a few familial cases have been documented (McKusick 182410) [18, 20, 22-24].

We report a familial aggregation of SS of apparently autosomal dominant inheritance associated with various clinical vasospastic phenomena.

Case report and family history

The patient

A 40-year-old Arab woman presented with a progressive neurological disorder of 2 years’ duration following a right hemiplegia and dysphasia of sudden onset. After a minor initial recovery of the deficit, her condition continued to deteriorate and she developed emotional lability, drooling, dysphagia and left-handed clumsiness. The patient did not smoke and used no oral contraceptives or illicit agents. Her medical history was remarkable in that it in-
cluded a labile untreated hypertension, β-thalassaemia minor and mottled skin lesions noted by her family since the age of 30.

On examination, her blood pressure was 140/85 with no pulse deficit. A single retinal vessel sheathing was noted in the right eye. Skin changes consisted of a persistent LR most prominent over the buttocks, lower back, thighs and dorsal aspects of the arms and hands, and acrocyanosis. Neurological examination revealed a global dysphasia, saccadic pursuit more pronounced to the left, exaggerated gag and jaw reflexes, and pseudobulbar features. There was a spastic right hemiplegia, mild weakness of the left arm and generalized hyperreflexia with a bilateral Babinski sign.

Cerebrospinal fluid was acellular with a normal protein level, negative syphilis serology and no oligoclonal bands. EEG showed nonspecific slowing, mostly over the frontal areas. Brain CT demonstrated diffuse cortical atrophy and a left temporoparietal nemenhancing hypodense lesion consistent with an old infarction. MRI also showed bilateral ischaemic changes (Fig. 1). Aortic arch and cerebral four-vessel angiography disclosed a focal narrowing of the left middle cerebral artery (MCA) M-1 segment, occlusion of the left recurrent artery of Heubner and diminished opacification in the left MCA territory consistent with distal vessel involvement. Additional distal irregularities were identified in parietal and temporal branches of the right MCA.

Complete blood count, peripheral blood smear and haemoglobin electrophoresis were characteristic of β-thalassaemia minor. Erythrocyte sedimentation rate (ESR) was 50/80 and evaluation of serum iron showed a mild deficiency. Bleeding time and coagulogram were normal including proteins C and S, antithrombin III, and tests for lupus-like anticoagulant, anticardiolipin antibody and spontaneous platelet aggregation. Plasma fibrinogen was 507 mg/dl (normal range 200–400 mg/dl), and C-reactive protein (CRP) was trace positive. An automated chemical and enzymatic panel was normal except for a creatinine value of 173 mol/l (normal range 60–106 mol/l). Additional normal or negative relevant blood test results included: protein and immunoelctrophoresis, rheumatoid factor, antinuclear, anti-SS-A and anti-SS-B antibody titres, complement components 3 and 4, cryoglobulin, syphilis and hepatitis B serology. Lipoprotein electrophoresis showed low HDL cholesterol levels of 26 mg% (normal range 35–80 mg%). There was a trace proteinuria in urinalysis, and urine assays for oxalate and amino acids were normal. Chest radiography, ECG, upper gastrointestinal series and transoesophageal echocardiography were unremarkable. Abdominal ultrasonography disclosed a right kidney stone and mild hydronephrosis.

Histological examination of a skin biopsy specimen from the right thigh revealed partial occlusion of a small artery at the dermis-subcutis border (Fig. 2). This was brought about by a subendothelial "cushion" consisting of small regular cells with indistinct cell borders and acellular matrix bulging into the vessel’s lumen. Elastica-van Gieson stain demonstrated focal degradation of the internal elastic membrane and atrophic media. Other small arteries in the area showed only mild intimal proliferation. Smaller blood vessels (arterioles and venules) in the upper dermis were surrounded by cuffs of inflammatory cells, mainly lymphocytes, large mononuclear cells and a few polymorphonuclears. There were no perivascular infiltrates around the affected deep dermal arteries.

During the following year, the patient was treated with aspirin and dipyridamole and her condition remained stable.

The patient’s family (Fig. 3)

Five of the patient’s siblings underwent clinical examination and three exhibited various vasospastic skin phenomena. A 32-year-old brother (II.6) had Raynaud’s phenomena and two sisters (II.1,2), aged 45 and 43 years, manifested fixed LR. One of these sisters (II.1) had two transient episodes of left arm weakness at the age of 44 and has been on acetylsalicylic acid since then. None of these siblings had any identifiable cardiovascular risk factors, they were neurologically intact and refused further evaluation. Another sister (II.9) was reported to have mottled skin and acute right-sided paralysis with “speech arrest” at the age of 24. She had died before this fam...