Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy with severe factor XII deficiency

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PMID: 19934572
DOI: 10.4103/0028-3886.57806

Abstract

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited adult-onset microangiopathy caused by missense mutations in the Notch3gene on chromosome 19. However, common vascular risk factors may additionally modify clinical expression and progression of the disease. The role of various prothrombotic factors has also been implied. We report a case of a middle-aged man with typical clinical, neuroimaging and histological features of CADASIL, but with notably prolonged activated partial thromboplastin time. Hematological investigations revealed severe clotting Factor XII deficiency. This case illustrates that the occurrence of vascular risk factors should not be overlooked in patients with CADASIL.

Key words: *Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, factor XII deficiency, small vessel disease*

Introduction

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is an inherited nonatherosclerotic adult-onset microangiopathy caused by missense mutations in the Notch3gene on chromosome 19p13.[1] Altough common vascular risk factors in CADASIL are infrequent, it has been suggested that they may play a role in disease expression and progression.[2,3] An association with prothrombotic risk factors has been implied.[4] Clotting Factor XII (FXII) is a protease that, when activated, initiates the intrinsic pathway of blood coagulation, but also participates in bradykinin formation and activation of the fibrinolytic system. FXII deficiency has been associated with an increased risk of arterial and venous thromboembolic disease, especially at a young age, attributed to reduced plasma fibrinolytic activity.[5] We report a patient with typical clinical, neuroimaging and pathohistological features of CADASIL, associated with severe hereditary FXII deficiency.

Case Report

A 48-year-old man presented with a sudden onset of dysarthria and dysphagia. Two years previously he had experienced acute onset of dizziness and gait disturbance, which partially improved. His past history was unremarkable. Family history for migraine, arterial and venous thrombosis was negative. On admission, neurological examination revealed horizontal nystagmus to the right, pseudobulbar palsy and spastic bihemiparesis. Gait was spastic. Neuropsychological testing showed a mild frontosubcortical dysfunction. Patient had mild depression.

Routine blood cell counts, serum cholesterol, triglycerides, lipoprotein(a), fasting glucose and liver function tests were unremarkable. Cerebrospinal fluid biochemistry

protein and cell count were normal, and oligoclonal bands were not found. Vasculitis blood screen, including anticardiolipin antibodies, was negative. Levels of fibrinogen, prothrombin time and thrombin time were normal, but activated partial thromboplastin time (aPTT) was elevated (112 sec, reference 27-35 sec), with correction studies. Electrocardiogram, transthoracic and transesophageal echocardiography were negative. Carotid ultrasound was unremarkable. Supraaortic and cerebral angiogram was normal. Brain magnetic resonance imaging (MRI) revealed isolated and confluent ischemic changes in subcortical white matter (WM) and brainstem [Figure 1a and b].

The skin biopsy samples for ultrastructural investigation were fixed in cold 3% glutaraldehyde, postfixed in 1% osmium tetroxide and embedded in Epon. Semi-thin sections were stained with 1% toluidine blue. Ultrathin sections were mounted on copper grids, stained with uranyl acetate and lead citrate, and examined under an electron microscope (Philips 208 S). Diagnosis of CADASIL was confirmed [Figure 2].

Considerably prolonged aPTT necessitated further hematological investigations. FXII measured by the clotting method was $< 1\%$ (reference 60-150%), while clotting activity of Factors II, V, X, VIII, IX, XI and high molecular weight kininogen were normal. Presence of circulating inhibitor to FXII and presence of lupus anticoagulant was excluded by mixing studies with normal plasma and by addition of phospolipids to patient's plasma. Addition of equal part of normal plasma completely corrected prolonged aPTT in patient's plasma, but addition of phospholipids did not. Activities of antithrombin III, protein C, protein S, plasminogen and sensitivity to activated protein C were normal. Plasminogen activator inhibitor was 8.6 U/ml (reference 0.3-3.5 U/ml) and tissue-plasminogen activator 5.8 ng/ml (reference 1-10 ng/ml) indicating diminished fibrinolytic activity. Prothrombin fragment 1 + 2 (F 1 + 2) level was elevated (1.6 nmol/L; reference 0.4-1.1 nmol/L). Patient's mother and son had moderately decreased FXII levels (57% and 48% respectively), suggesting hereditary nature of deficiency. They were both asymptomatic and there were no indications for presence of consanguinity in patient's family.

Discussion

The association of CADASIL and FXII deficiency has not been reported before. Our patient had clinical, neuroimaging and pathohistological findings typical for CADASIL, but markedly prolonged aPTT led to detection of severe FXII deficiency. Although this patient lacked history of migraine and family occurrence of the disease, CADASIL phenotype variety in this regard has been recognized.[2] CADASIL diagnosis was confirmed by skin biopsy. The reported diagnostic specificity for skin biopsy has been 100%.[1] Other etiologies for ischemic stroke and WM lesions were excluded with extensive investigations.

Severely decreased FXII clotting activity and familial occurrence of deficit correspond to homozygous or double heterozygous FXII deficiency. An increased frequency of FXII deficiency was found in patients with recurrent arterial thromboembolism and/or myocardial infarction.[5] Recently, low FXII levels have been associated with an increased risk of coronary artery disease and stroke in middle-aged men.[6] Interestingly, cases with ischemic stroke are infrequently reported, and additional congenital or acquired thrombotic risk factors are often identified.[7,8] A significant number of

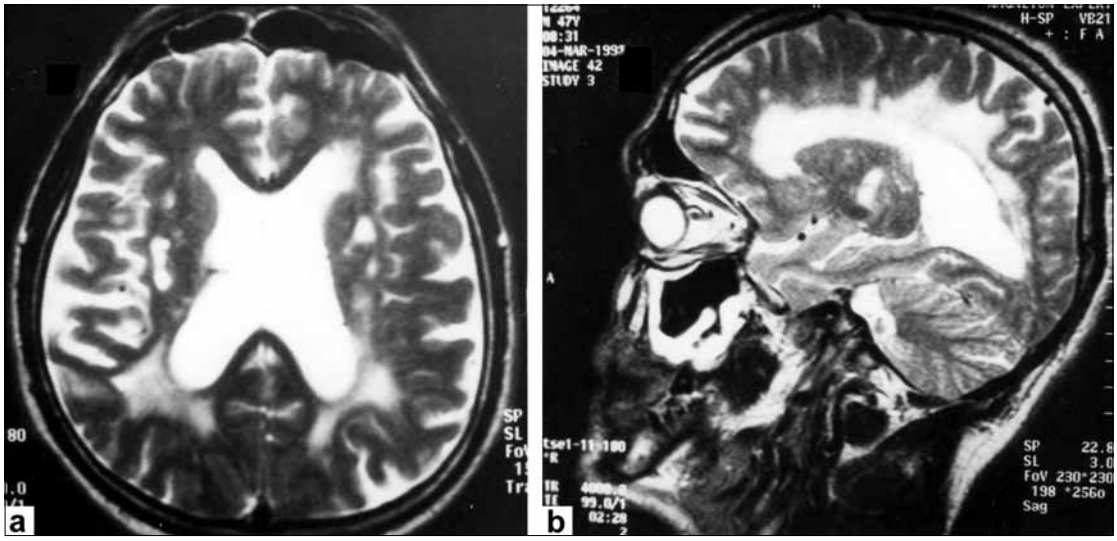

Figure 1: MRI T2-weighted brain images (a) axial scan; (b) sagittal scan; multiple areas of high intensity in subcortical and periventricular white matter

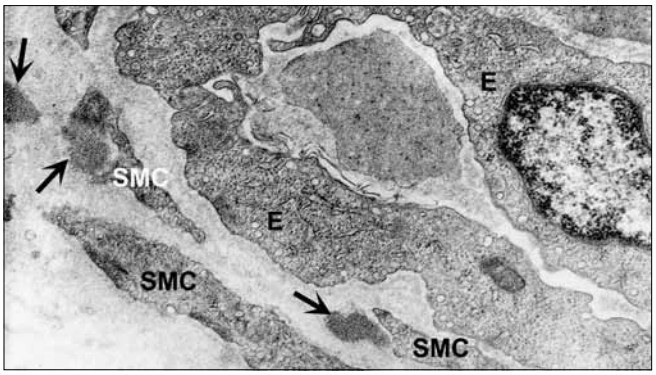

Figure 2: Skin histopathology; Skin arteriole, electron micrograph (×16,000) ; E-endothelial cells; SMC - smooth muscle cells; black arrows - granular osmiophilic material

individuals with severe FXII deficiency never develop thrombosis, which may be indicate that additional contributing factors are lacking in these cases.

To the traditional view, vascular risk factors are unremarkable in CADASIL cases.[4] However, the lack of strong genotype-phenotype correlation in CADASIL implies involvement of modifying factors.[2] Higher age and blood pressure are independently associated with a larger volume of T2-visible lesions and progressive brain volume loss.[3,9] Current smokers suffering from CADASIL experience stroke at an earlier age, potentially due to induction of a prothrombotic state.[2]

Prothrombotic risk factors and CADASIL have been linked before. Pantoni and co-workers[4] reported three CADASIL patients with hyperhomocysteinemia, elevated levels of lipoprotein(a) and positive antiphospholipid antibodies, which were negative in our patient. In one study plasma homocysteine levels were higher in CADASIL patients than in those with ischemic strokes due to other etiologies, but this was not observed by other authors.[2]

Gene for FXII is mapped on chromosome 5q33, and it is possible that the presence of both CADASIL and FXII deficiency was coincidental in our patient, and that cerebral small vessel disease was solely secondary to CADASIL. However, interactions between prothrombotic and genetic factors may have had a synergistic effect on the cerebral microvasculature in our patient, jointly causing small vessel arteriopathy.

Coexistence of vascular risk factors in a patient with typical presentation does not exclude the diagnosis of CADASIL. Potential role of prothrombotic factors in CADASIL pathogenesis needs to be explored in larger studies.

Acknowledgment

This work has been supported by the Ministry of Science, Republic of Serbia (Project no. 145025D and no. 145061).

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Accepted on 02-07-2009
Source of Support: Ministry of Science, Republic of Serbia (project no. 145025D and no. 145061), **Conflict of Interest:** None declared.