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Homozygous C677T mutation of the 5,10-methylenetetrahydrofolate reductase gene with hyperhomocysteinaemia associated with lupus anticoagulant in a chronic peritoneal dialysis patient with cerebral venous thrombosis

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ABSTRACT

We report a case of a cerebral venous thrombosis (CVT) in a chronic kidney disease patient with three CVT predisposing conditions. A 53 year-old woman on chronic peritoneal dialysis presented to the emergency department with acute headache and vertigo. The neurological examination and head CT scan performed at the emergency department were normal but, three days later, a lateral gait deviation and a horizontal nystagmus were identified. A brain MRI and MRI-venogram confirmed a left lateral sinus thrombosis. Hormonal replacement therapy (HRT), a positive lupus anticoagulant and a homozygous mutation on the methylenetetrahydrofolate reductase gene, with hyperhomocysteinaemia, were the three well-known prothrombotic conditions identified in this patient. HRT was discontinued, the patient started anticoagulation with warfarin and folic acid supplementation and was discharged, 10 days after admission, complaining of a mild vertigo. After six months of therapy the patient had vertigo improvement and maintained a positive lupus anticoagulant. The head MRI and MRI-venography showed a thrombus reduction.

The rather unexpected finding of three CVT predisposing conditions in this patient stresses the need of a broad diagnostic approach in CVT. The diagnosis of antiphospholipid syndrome implies life-long anticoagulation.

Key-Words:
Cerebral venous thrombosis; hyperhomocysteinaemia; lupus anticoagulant; peritoneal dialysis.

CASE PRESENTATION

A 53 year-old female patient presented to the emergency department in March 2004 with an intense,

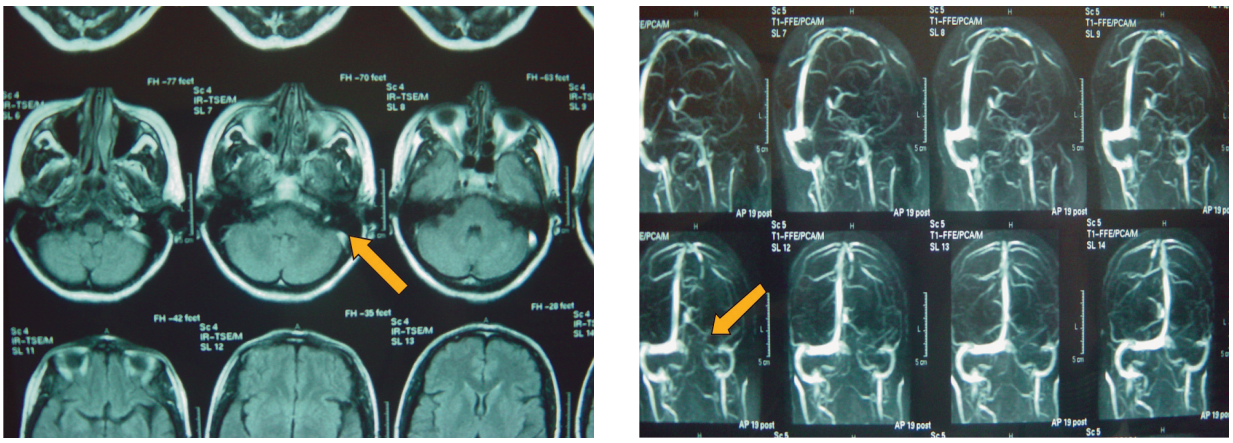

Figure 1

MRI and MRI venogram. Left lateral sinus thrombus (arrows).

constant, occipital headache aggravated with Valsalva manoeuvers and associated with vertigo, nausea, vomiting and gait disturbance. This severe headache had been preceded a day earlier by a milder, unilateral, pulsatile headache, similar to previous migraine crisis. The patient had a prior history of hypertension, migraine, autosomal dominant polycystic kidney disease (APKD), with a negative family history for cerebral aneurysms, and she had been on automated peritoneal dialysis (APD) since April 2003. She denied any previous venous or arterial thrombosis or any obstetric complications but was on hormonal replacement therapy with transdermal oestrogen.

Physical examination revealed an alert and orientated patient, with normal vital signs. Neurological and otorhinolaryngological examinations were normal. Laboratory tests were normal except for a prolonged partial thromboplastin time (29/27 seconds) and the expected elevation of serum creatinine and urea levels. Head CT Scan was normal and the patient was admitted to the Nephrology department.

Three days later, the patient was still symptomatic and a second neurological evaluation revealed a lateral gait deviation and horizontal nystagmus, with a right fast component. She then underwent a brain MRI and venogram-MRI (Fig. 1) that revealed a left lateral sinus thrombosis and excluded cerebral aneurysms or vascular malformations. Thrombophilia evaluation demonstrated a positive lupus anticoagulant and hyperhomocysteinaemia (22 μmol/L) associated with a homozygous VAL/VAL mutation on the 5,10-methylene--tetrahydrofolate-redutase (MTHFR) gene (Fig. 2) and low seric folate levels. Activated protein C resistance, factor V Leiden, G/A 20210 prothrombin gene mutation, antithrombin III, protein C and protein S deficiencies and other antiphospholipid antibodies were excluded. Systemic lupus erythematosus serology was negative.

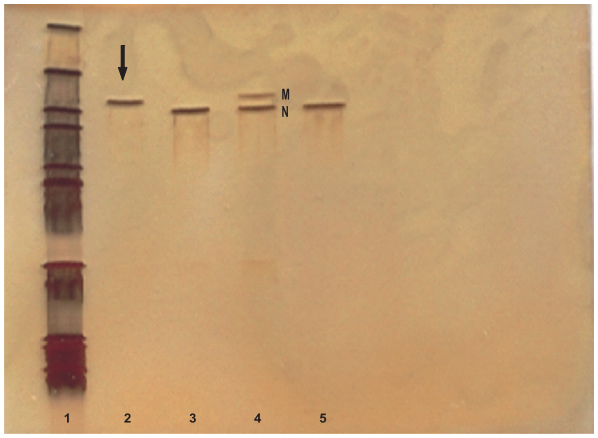

Figure 2

Polymerase Chain Reaction (PCR) analysis of MTHFR 677C/T allele polymorphism (or VAL-VAL mutation). Amplification with PCR followed by digestion with a restriction enzyme *Hinf* I. After digestion the PCR products were subjected to electrophoresis in acrilamide gel coloured with silver staining: *Hinf* I digested PCR fragments from the 677C/T mutation (M) and from the normal alelle (N). Lane1 – Molecular weight marker; Lane 2 – 677C→T homozygous (arrow); Lane 3 – wild type (2 normal alelles); Lane 4 – 677C→T heterozygous and Lane 5 – PCR (undigested control fragment).

The patient initiated therapy with enoxaparin, warfarin and acid folic supplementation. Hormonal replacement therapy was discontinued. There was a progressive clinical improvement and the patient was discharged ten days later with mild vertigo and receiving warfarin (INR target of 2-3) and oral folic acid. After 6 months, the patient had vertigo improvement and the MRI and venography-MRI (Fig. 3) demonstrated a thrombus reduction and permeabilisation of the left lateral sinus.

DISCUSSION

CVT is a rare condition[1] that results from a complete or partial occlusion of a cerebral vein or cerebral dural sinus by a thrombus. Venous obstruction may lead to cerebral parenchyma infarction, which was not the case in our patient. The superior sagital sinus (62%), left lateral sinus (44.7%) and right lateral sinus (41.2%) are the most frequently occluded venous sinus and in 50% of cases it is possible to demonstrate the involvement of multiple sinus[2].

Cerebral venous thrombosis has an estimated annual incidence[3] of three to four cases in 106 individuals. In the International Study on Cerebral Vein Thrombosis (ISCVT), the 624 patients had a mean age of 39 years old and 75% were female. Other studies[4] confirmed the higher prevalence of CVT in women, particularly those aged 20 to 35 years old.

In the ISCVT, 87.5% of patients had CVT risk factors and in 43.6% they were multiple. Thrombophilia (34.1%), oral contraceptives (54.3%), pregnancy-puerperium (20.1%), neoplasia (7.4%) and infections (12.3%) (e.g. ear-nose-throat, central nervous system) were within the most prevalent prothrombotic conditions identified. Our patient had at least three recognised predisposing conditions to CVT (lupus anticoagulant, hyperhomocysteinaemia and hormonal replacement therapy).

CVT belongs to the spectrum of neurological manifestations of antiphospholipid syndrome[5] and its association with lupus anticoagulant is well described[6-9], although it is seldom the first manifestation of antiphospholipid syndrome in a middle-aged patient. Martinelli *et al* [10] have demonstrated that hyperhomocysteinaemia is associated with an increased risk for CVT. Hyperhomocysteinaemia is prevalent in chronic kidney disease patients, which is probably related to a reduction in the renal clearance of seric homocysteine[11]. Some forms of MTHFR gene mutation[11], namely the homozygous MTHFR 677C/T mutation diagnosed in this case, have a greater impact in homocysteine levels elevation in the context of low folate levels, and supplementation with folic acid is a logical intervention in patients with these findings.

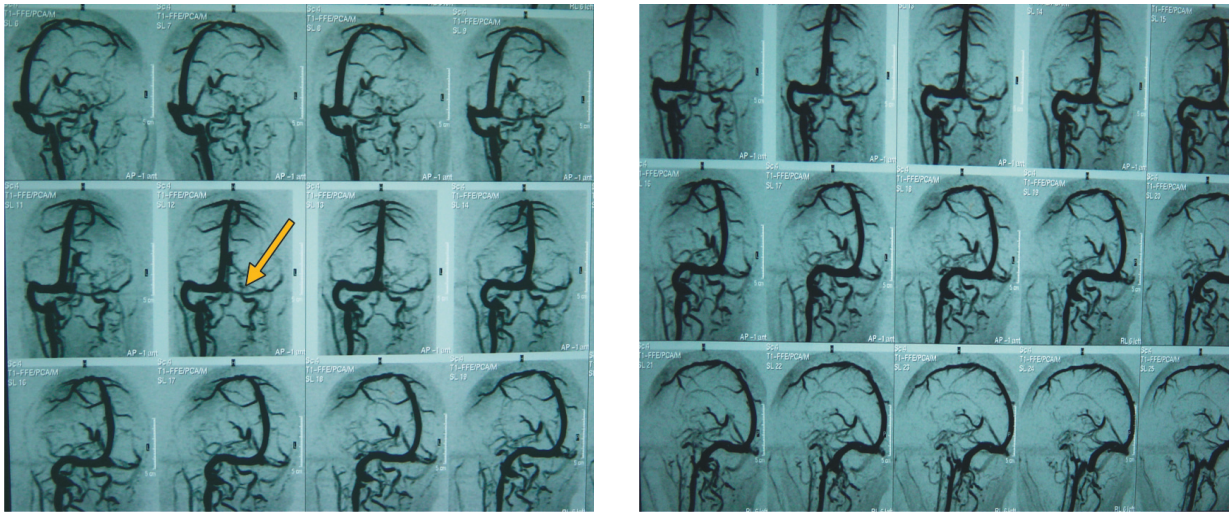

Figure 3

MRI venogram at 6 months. Partial recanalisation of left lateral sinus (arrow).

Various drugs have been associated with CVT, namely oral contraceptives[2,12-14] and hormonal replacement therapy[15]. In the ISCVT, 54.3% of the 381 female patients aged below 50 were on oral contraceptives. Oral hormonal replacement therapy (HRT) is associated with a state of activated C protein resistance, not related with factor V Leiden, which may predispose to venous thrombosis[15,16]. Although this has not been demonstrated in transdermic HRT, it seemed adequate to discontinue the HRT in this patient.

Clinical manifestations of CVT are extremely variable. CVT may have an acute (37.2%), sub-acute (55.5%) or a chronic (7.2%) presentation and headache (88.8%), with convulsion (39.4%) and paresis (37.2%) the most frequent clinical manifestations identified[2]. Our patient had a clinical presentation of intracranial hypertension associated with vertigo. In 23% of ISCVT cases the clinical presentation is that of an intracranial hypertension. Vertigo, however, is a rare symptom of CVT and in our patient, it was probably related to vestibular dysfunction due to venous flux obstruction of the VIII cranial nerve.

CVT is diagnosed by identifying the thrombus and occlusion of the sinus by MRI, venography-MRI or cerebral angiography. Head CT scan is usually non-diagnostic and associated with a significant percentage of false-negatives[18], as was the case in our patient.

Treatment of CVT involves anticoagulant therapy, symptomatic treatment, with anticonvulsivants and analgesics, measures to reduce intracranial hypertension and aetiological treatment (e.g. infection). Non-fractionated intravenous heparin or subcutaneous low-molecular weight heparins can be used initially followed by oral anticoagulation. Local thrombolytic therapy is reserved for patients with clinical deterioration despite conservative therapy[19]. Our patient was treated with enoxaparin followed by warfarin with clinical improvement. We adjusted warfarin doses to an INR target of 2 to 3 based on recent reports[20,21] which showed that this is a safe approach.

The diagnosis of antiphospholipid syndrome implied the recommendation of life-long therapy with warfarin and regular screening with brain MRI and veno-MRI for assessment of the venous thrombus evolution and development of cerebral aneurysms (APKD). Discontinuation of HRT and supplementation with folate were other therapeutic measures in this case.

CVT has traditionally been associated with a bad prognosis, although recent studies have changed this perspective. In ISCVT, nearly 60% of the patients were completely asymptomatic and the mortality rate was 8.3%, in a median follow-up period of 16 months.

This CVT clinical case presented with several singularities worth stressing. First, the need to thoroughly evaluate a patient with acute headache and to exclude CVT even in the presence of a normal CT scan. Second, the finding of three predisposing factors to CVT in this patient, reflecting the need for a systematic and broad diagnostic approach. Evaluation of thrombophilia had a significant impact and implied the recommendation of permanent anticoagulation and supplementation with oral folate. Finally, the use of the minimum efficacious dose of oral anticoagulant is important to lessen the increased risk of haemorrhagic complications (e.g. haemocyst) in this patient.

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Conflicts of interest. None declared.

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