

CEREBRAL VEIN THROMBOSIS AND C677T POLYMORPHISM OF MTHFR WITHOUT HYPERHOMOCYSTEINEMIA: CASE REPORT

Trombosi venosa cerebrale e polimorfismo C677T di MTHFR in assenza di iperomocisteinemia: un caso clinico

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SUMMARY

One of the risk factors involved in Cerebral Venous Sinus Thrombosis (CVST) is the polymorphism C677T in both alleles of the methylene tetrahydrofolate reductase MTHFR gene.

We report one patient with CVST in which this risk factor does not correlate with hyperhomocysteinemia. We therefore propose that, in this case, several acquired factors, i.e. ulcerative colitis, corticosteroids and sickle cell anemia, may have played a key role in precipitating the cerebral vein thrombosis.

Key words: Cerebral Vein Thrombosis, MTHFR gene mutation, Hyperhomocysteinemia.

RIASSUNTO

Uno dei fattori di rischio coinvolti nell'insorgenza della trombosi venosa dei seni è il polimorfismo C677T per entrambi gli alleli del gene dell'enzima metilene tetraidrofolatoriduttasi. Noi riferiamo il caso clinico di una paziente affetta da trombosi venosa dei seni che non presenta iperomocisteinemia. In questo caso noi abbiamo ipotizzato che i fattori di rischio acquisiti quali la rettocolite ulcerosa, il trattamento con corticosteroidi e

l'anemia falciforme potrebbero giocare un ruolo determinante nel determinismo della trombosi venosa cerebrale.

Parole chiave: Trombosi venosa cerebrale, mutazione del gene MTHFR, iperomocisteinemia.

Introduction

Thrombosis of the cerebral veins and sinuses is a distinct cerebrovascular disorder that, unlike arterial stroke, most often affects young adults and children. It is a worrying condition because of the severity of the clinical manifestations and the high mortality rate, estimated at 5%-30%. The symptoms and clinical course are highly variable. The estimated annual incidence is 3 to 4 cases per 1 million population and up to 7 cases per 1 million among children. About 75% of the adult patients are women. In about 70% of cases the cause is identifiable, and may be infection, trauma, neoplasm or autoimmune disease [1]. Cerebral Venous Sinus Thrombosis (CVST) may also be associated with genetic prothrombotic conditions or coagulopathies i.e. deficit of antithrombin III, protein C or protein S, mutation of the genes for factor V or II [2, 3], resistance to activated protein C, prothrombin mutation (the replacement of A for G at position 20210), acquired prothrombotic states (i.e. nephrotic syndrome, antiphospholipid antibodies, hyperhomocysteinemia, pregnancy, puerperium), hematologic conditions (i. e. polycythemia, thrombocytopenia, leukemia, anemia) and drugs (i. e. oral contraceptives, asparaginase).

During the past decade, increased awareness of the diagnosis, improved neuroimaging techniques, and more effective treatment have improved the prognosis. To understand the symptoms and signs of sinus thrombosis, two different mechanisms should be distinguished: thrombosis of the cerebral veins with local effects caused

by venous obstruction, and thrombosis of the major sinuses which causes intracranial hypertension. In the majority of patients, these two processes occur simultaneously.

Case report

A 39-year-old woman visited our hospital because of sub acute onset (one week) of severe headache with left orbital location, pain on the first branch of left trigeminal nerve and left eyelid drop with diplopia. The general physical examination was normal. On admission, neurological examination showed a paresis of the left third cranial nerve with normal pupil size and the presence of lateral gaze nystagmus. In our patient no seizures or any epileptic disorder after admission was detected. She also suffers from mild inflammatory bowel disease (ulcerative colitis), hypothyroidism and sickle-cell anemia. Moreover, from few years before admission, steroid therapy had been prescribed to prevent a relapse of ulcerative colitis.

There was no history of hypertension, cigarette smoking, oral contraceptive assumption and recent pregnancy. MR angiography of the brain showed a complete occlusion of the left transverse and sigmoid sinuses (Fig. 1a). Diagnosis of CVST was thus confirmed. In the acute phase, routine blood count did not show a leucocytosis and basic biochemistry did not show an increase of inflammatory indices. Plasma levels of protein C, protein S, antithrombin III (AT III), antiphospholipid antibodies (ApA), anti-DNA antibodies, neutrophil cytoplasmic antibodies (ANCA), antinuclear anti-

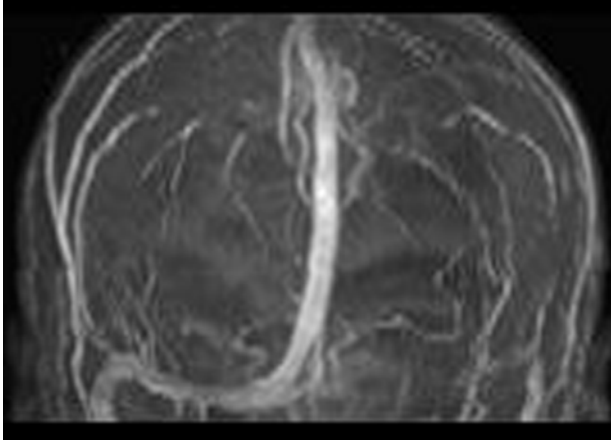


Fig. 1A: MR angiography of the brain showed a complete occlusion of the left transverse and sigmoid sinuses.

bodies, lupus anticoagulant antibodies, anticardiolipin antibodies, D-dimer value and homocysteine (5.8uM/l; v.n. 4.8-12.44uM/l) were detected and found normal. Factor II and V Leiden mutation and prothrombin mutation PAI1 (4G/5G polymorphism) were absent.

The C677T polymorphism in both alleles of the methylene tetrahydrofolate reductase MTHFR gene was present. The patient was given antibiotic and analgesic drugs. Intravenous (i. v.) heparin treatment was also associated, starting with a bolus of 80 I.U./Kg, followed by 17 I.U./Kg/24hours for 5 days; dosage was adjusted in order to maintain PTT value double than normal. She was also treated with prednisolone to prevent a relapse of ulcerative colitis.

After five days, MR angiography showed an initial but meaningful patency of the occluded sinuses (Fig. 1b).

Heparin treatment was followed by oral anticoagulant treatment for six months, to prevent clot propagation or recurrent thrombosis. Over this period INR was maintained between 2 and 3.

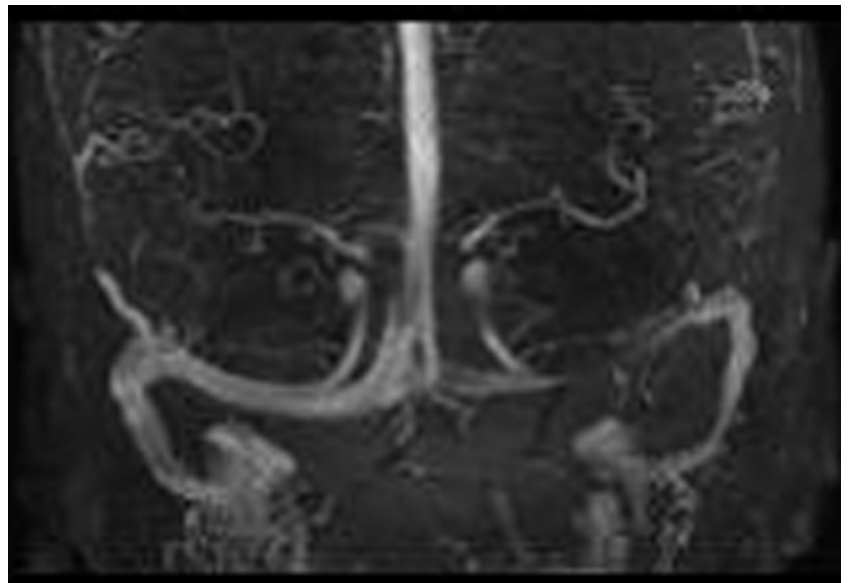


Fig. 1B: MR angiography showed an initial but meaningful patency of the occluded sinuses.

At an eight months follow up the patient was re-assessed through a complete neurological examination which was normal.

Discussion

The main finding of the present study is a good neurological short term outcome in our patient. This is in agreement with literature data, showing a favourable outcome in most patients experiencing CVST [2]. Moreover our patient underwent MR angiography to confirm the diagnosis. In fact MRI and MR angiography are currently reputed as the best diagnostic tool for CVST [3]. Infection/inflammation is a condition that may predispose to brain arterial or venous thrombosis [8]. Coagulation anomalies are established risk factors for deep vein thrombosis. Thrombophilic factors, such as deficits in antithrombin III, protein C and protein S are described in some patients with cerebral vein thrombosis. The correlation between protein C levels and the risk of CVST is not yet precisely defined. The common finding of asymptomatic people (evaluated in 1:500 healthy blood donors) who carry a

hereditary heterozygous protein C deficiency [6, 7], raises the possibility that this defect alone may not be a sufficient prothrombotic factor unless other co-morbid conditions are present. Deep vein thrombosis has been associated with mild-to-high circulating levels of homocysteine. Hyperhomocysteinemia may be a risk factor for CVST [9]. CVST has been reported associated with mutations in the prothrombin gene and the factor V gene [4, 5]. Hyperhomocysteinemia has also been reported in three overweight women with cerebral venous thrombosis, but in one of these a prothrombin mutation was present and in the remaining two MTHFR mutation was present on one allele only [10]. Association between hyperhomocysteinemia and the C677T polymorphism in both alleles of MTHFR was reported in literature [11].

The C677T polymorphism in both alleles of the methylene tetrahydrofolate reductase MTHFR gene was present in our patient but without hyperhomocysteinemia. This fact confirms the necessity of not only a careful follow up of thrombophilic condition, but also genetic follow up to claim for a causal relationship in the pathogenesis of CVST.

Moreover, MTHFR mutation is not very rare and could be an innocent bystander.

In this case several acquired factors, i.e. ulcerative colitis, corticosteroids but principally sickle cell anemia, may have played a key role in precipitating the cerebral vein thrombosis, in fact while the finding of MTHFR polymorphism (with or without hyperhomocysteinemia) is not a noticeable condition in CVST, sickle cell ane-

mia is a more probable and interesting aetiological factor [12, 13, 14, 15].

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