

Simultaneous tromboembolic events in a patient with heterozygous MTHFR mutation

CASE REPORT

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Abstract

Background: Hyperhomocysteinemia is a well recognised risk factor for arterial and venous thrombosis. The most common form results from methylenetetrahydrofolate reductase (MTHFR) gene mutations leading to decreased enzymatic activity.

Case report: We present the case of a 34 year-old woman with a sudden onset of left hemiparesis and aphasia accompanied by retrosternal pain. She is diagnosed with acute posteroinferolateral myocardial infarction and stroke. Homocysteine level was determined and it was moderately elevated. The coronary angiogram revealed partially recanalised embolic occlusion of posterior left ventricular branch and posterior interventricular artery. A conservative treatment management is adopted. She remained haemodynamically stable, with complete resolution of neurological symptoms and evolution to subacute myocardial infarction.

Conclusions: The particularity of our case is represented by simultaneous thromboembolic events causing myocardial infarction and ischemic stroke in a patient with a history of recurrent pregnancy loss, which was previously diagnosed with MTHFR gene mutation. Moderate hyperhomocysteinemia, also found in our patient, is recognised as an etiopathogenic factor of thrombophilia. The right diagnosis and therapeutic approach could be the key to improved prognosis in this category of patients. MTHFR gene mutation causing hyperhomocysteinemia should be suspected in patients with thromboembolic events, especially when occurring repeatedly or at young ages.

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Introduction

Thrombophilias are conditions associated with hypercoagulable status and increased risk of arterial and venous thrombosis, which represents a significant cause of mortality and morbidity worldwide [1]. The prothrombotic states may be inherited or acquired, but also due to genetic and environmental interactions [2]. Investigating for thrombophilia requires an initial evaluation of classical prothrombotic risk factors such as smoking, dyslipidemias, arterial hypertension or diabetes mellitus. Extended profile of investigations is necessary in patients with arterial or venous thrombosis which occur repeatedly, in unusual sites or at young ages, when family aggregation of thrombotic events is identified, as well as in women with recurrent idiopathic pregnancy loss. It must include a complete blood count and erythrocyte sedimentation rate, a blood film examination, prothrombin time (PT) and activated partial thromboplastin time (aPTT), factor V Leiden, antithrombin and fibrinogen levels, protein C and S, prothrombin gene mutations, homocysteinemia, methylenetetrahydrofolate reductase (MTHFR) gene mutations and antiphospholipid antibodies [3].

Homocysteine has been recognised as a cardiovascular risk factor besides the traditional ones such as smoking, obesity, diabetes mellitus and arterial hypertension, in line with the observations made in patients with homocystinuria [4-6]. This is an inborn error of methionine metabolism caused by deficient activity of cystathionine β -synthase (CBS) and thereby impairment of the transsulphuration pathway leading to excessive accumulation of homocysteine [7, 8]. Numerous studies have demonstrated the early onset and rapid development of arteriosclerosis in patients with homocystinuria. Moreover, thromboembolic events, both arterial and venous have been reported, which represent the main life threatening complication at young ages [4, 8-11].

Experimental data suggested the mechanisms responsible for atherogenic and thrombogenic effects of high homocysteine levels: induces oxidative stress

and vascular inflammation, promotes endothelial dysfunction as a result of increased asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO-synthase, reduces bioavailability of nitric oxide, alters lipoprotein metabolism, produces vascular hypertrophy in the microcirculation, stimulates tissue factor expression in monocytes, increases platelet aggregation and interferes with several clotting factors [12-16]. A new study demonstrated that hyperhomocysteinemia exacerbates vascular constrictive remodelling after arterial balloon injury by accelerated neointima formation and collagen accumulation in the adventitia [17].

Homocysteine concentrations are determined by synergistic action of genetic and nutritional factors such as serum folate, riboflavin and cobalamin [18-20]. It appears to be also influenced by physiological factors (dietary habits, male sex, menopause, alcohol and coffee intake, smoking, increased muscle mass), diseases (reduced glomerular filtration rate and overt renal failure, hypothyroidism, diabetes mellitus, psoriasis) and drugs [16, 20].

Methylenetetrahydrofolate reductase (MTHFR) is involved in homocysteine metabolism and catalyzes the conversion of 5,10-methylenetetrahydrofolate (5,10 MTHF) to 5-methyltetrahydrofolate. This serves as a methyl donor in the subsequent homocysteine remethylation to methionine, reaction catalyzed by methionine synthase (MS) and requiring cobalamin as a cofactor [21]. It is also acknowledged that MTHFR plays a role in distributing folate species either towards homocysteine remethylation as depicted above, or to nucleic acids biosynthesis [21, 22]. Two common MTHFR gene polymorphisms have been identified: C677T and A1298C. C677T polymorphism results from C \rightarrow T transition at nucleotide 677 in exon 4 and produces an alanine to valine amino acid substitution in the biomolecular structure [23, 24]. The incidence of homozygous mutation (TT) in general population varies between 5 and 12% [25-28]. The heterozygous mutation has an incidence of 25-40%

[29]. The C677T mutation produces a thermolabile variant of the enzyme characterized by decreased catalytic activity and hyperhomocysteinemia. In comparison with the wild type allele, the residual enzyme activity is as low as 30 to 50% in homozygotes and 65% in heterozygotes [30-32].

Case report

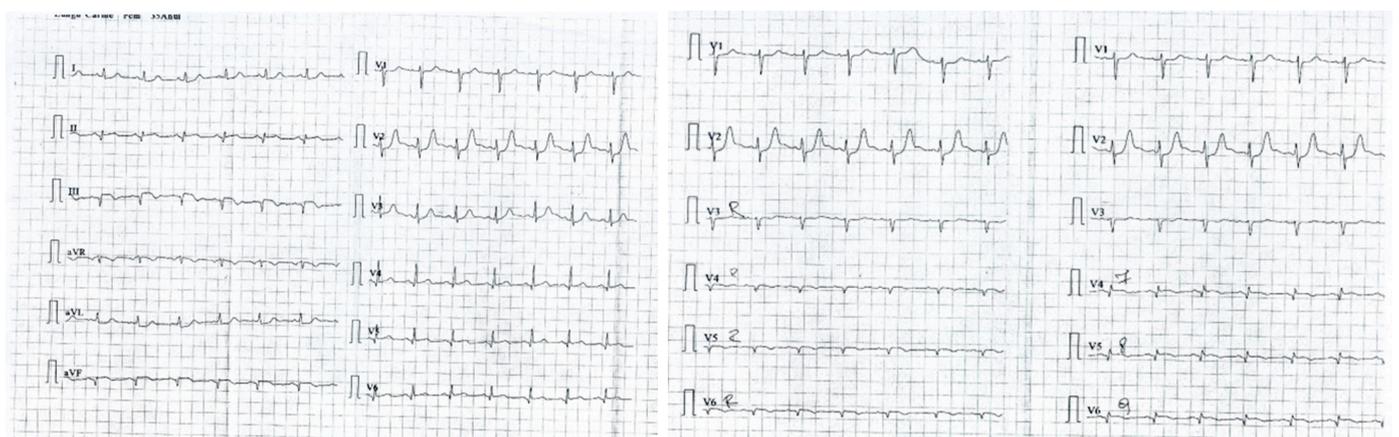
We present the case of a female patient from urban environment, aged 34, with a remote smoking history of 5 pack-years, who reported no drinking or drug use and without significant family history. The patient's medical history was notable for obstetrical events consisting of two pregnancies (at age 29 and 31) that ended at an unknown gestational age and the reason was not determined. Eighteen months ago she had a stillbirth occurring in a full-term pregnancy. Shortly after she was tested for thrombophilia and the heterozygous C677T mutation of MTHFR gene was discovered. At the time treatment with aspirin, folic acid and omega 3 fatty acids was recommended, but the patient interrupted it after two months.

The patient had been well until the day of admission, when she reported sudden onset of left hemiparesis and motor aphasia, strongly suggestive of right hemisphere stroke. Non-contrast computed tomography was performed within 2 hours from presentation and showed no images consis-

tent with intracerebral infarction or hemorrhage. Shortly after the investigation and before starting anticoagulant therapy the patient reported sudden development of retrosternal pain of medium intensity, occurring at rest and lasting longer than 30 minutes. The electrocardiogram showed ST segment elevation and Q waves in inferior leads and correlated with raised myocardial biomarkers (creatinine-kinase MB 166 u/L, TroponinT 7.72 ng/mL, ASAT 288 u/L, LDH 1438U/L). She was referred to a cardiologist.

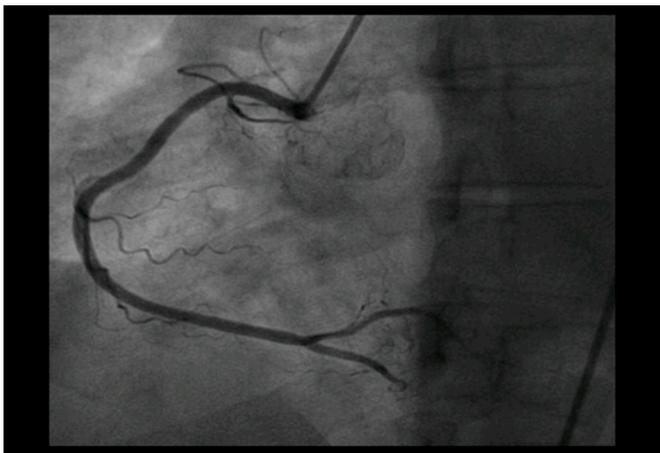
On examination the patient is haemodynamically stable, blood pressure (BP) 120/70mmHg at both arms, heart rate (HR) 80, rhythmic heart sounds without additional murmurs and normal oxygen saturation. The neurological examination revealed minimal motor deficit, paresthesia and weakness of the left arm and no aphasia. The ECG aspect is consistent with the diagnosis of acute posteroinferolateral myocardial infarction with ST segment elevation (**Fig.1**). Ecocardiography revealed undilated left ventricle with preserved global systolic function, with an ejection fraction of 50%, normal contractility except for akinesia of the mediobasal segment of the inferior wall. There are no signs of pericardial effusion, intracavitary thrombi, atrial dilation, diastolic dysfunction, valvular disease or pulmonary hypertension and the right ventricle is normal.

Figure 1: Acute posteroinferolateral ST elevation myocardial infarction.



The patient underwent emergency coronary angiography for non-ST-segment elevation myocardial infarction which revealed partially recanalised embolic occlusion of posterior left ventricular branch and posterior interventricular artery (**Fig.2**). A conservative treatment strategy is adopted and anticoagulant therapy with unfractionated heparin is immediately started. Dual antiplatelet therapy (aspirin plus clopidogrel) and high-dose statin (atorvastatin) are associated. Spironolactone is added later on and is preferred as anti-remodelling agent due to low blood pressure values.

Figure 2: Partially recanalised embolic occlusion of posterior left ventricular branch and posterior interventricular artery.



A new computed tomography of the brain is performed in the fifth day after admission. It revealed a cortico-subcortical hypodense area, 40/29mm, located in the temporo-parietal right hemisphere, suggestive of subacute ischemic stroke.

Further testing for thrombophilia was recommended in order to rule out causes of acquired prothrombotic states. The titres of antinuclear antibodies and their subsets, as well as antiphospholipid antibodies were within the normal range. Homocysteine plasma concentration has also been determined and it was moderately raised (32 $\mu\text{mol/L}$).

Under treatment she remained haemodynamically stable, experienced no recurrent anginal pain and

had a complete resolution of neurological symptoms within three days from admission. Repeated ECG showed evolution to subacute myocardial infarction aspect and transthoracic echocardiogram at discharge revealed a slight improvement of inferior wall contractility with residual hypokinesia of the medio-basal segment. The patient is discharged home after 12 days of hospitalization with the main diagnosis of acute posteroinferolateral myocardial infarction with conservative treatment and acute temporo-parietal ischemic stroke, both due to thromboembolic events in the context of thrombophilia.

Discussion

The mechanism by which MTHFR gene mutations produce prothrombotic states is represented by elevated levels of plasma homocysteine due to decreased enzymatic activity of methylenetetrahydrofolate reductase. This effect is amplified by all the above mentioned factors, especially low concentrations of serum folate and vitamins B complex. However, data from literature are inconsistent and insufficient.

Numerous studies have demonstrated an increase in cardiovascular risk in the presence of elevated levels of homocysteine [30-35]. Discordant results have been found in prospective studies, some of them showing strong associations and some of them none [35]. A meta-analysis of 30 prospective and retrospective studies showed that 25% lower homocysteine levels was associated with 11% lower ischemic heart disease risk and 19% lower stroke risk, suggesting an independent role of homocysteine as a cardiovascular risk factor, albeit modest [36]. Another meta-analysis demonstrated a weak, but significant association between homocysteinemia and coronary heart disease risk in prospective studies and a more robust association when correlated with cerebrovascular disease [37].

Data from literature indicate the association between moderately raised homocysteinemia and atherothrombosis risk, nevertheless in our patient no underlying atherosclerotic lesions have been found, pointing out a thromboembolic mechanism, both for stroke and myocardial infarction.

Medical data strongly affirm the association of severe hyperhomocysteinemia with high cardiovascular risk. However, regarding moderate or mild elevations in homocysteine levels, determined most frequently by MTHFR gene mutations, the results of the studies are discordant [38-46]. In this case, simultaneous ischemic events occurred in a patient with no overt classical risk factors. Although moderately elevated, hyperhomocysteinemia due to MTHFR mutation, previously identified in this patient, has been responsible for concurrent thromboembolic stroke and myocardial infarction.

There is debate about the existence of a real causal relationship between hyperhomocysteinemia per se and the cardiovascular outcomes. Although most of the studies demonstrate the association, little evidence is available to support the direct causality, relationship [44, 47, 48]. Although several pathogenic effects of hyperhomocysteinemia have been evidenced, the following uncertainties emerged: is hyperhomocysteinemia merely associated with classical risk factors like smoking, dyslipidemias, arterial hypertension, thus creating confusion regarding its independent role in atherogenesis and thrombogenesis; is hyperhomocysteinemia an effect of atherosclerosis and/or acute vascular events rather than a causative agent [47-50]; the existence of subclinical premature renal impairment in atherosclerosis patients, thereby affecting homocysteine clearance [47, 49, 51]. Therefore it has been postulated that homocysteine is at most a marker of cardiovascular risk rather than an ethiological factor. Studying the correlation between MTHFR genotypes and cardiovascular risk has been proposed in order to demonstrate

that a cause of chronic hyperhomocysteinemia is associated implicitly with high cardiovascular risk, therefore supporting the direct causality relationship [44, 47].

MTHFR gene mutation carriers have a decreased enzymatic activity and higher levels of homocysteine which are inversely related to folate status. A meta-analysis including 40 studies, both retrospective and prospective, demonstrated a 16% higher risk of developing coronary heart disease in patients with MTHFR 677TT genotype and a trend toward increased risk in heterozygous patients (CT genotype) compared the normal genotype (CC). It also showed that the risk is high only in patients with low folate status [44]. Significant higher risk of ischemic heart disease, deep vein thrombosis and stroke associated with MTHFR-TT genotype has been found in another meta-analysis including 92 studies, concluding that this correlation provides evidence for direct causality between hyperhomocysteinemia and cardiovascular disease [38].

Recurrent pregnancy loss represents a health issue affecting up to 5% of women of reproductive age [52]. The ethiological factors include uterine anomalies, endocrinologic disorders such as hypothyroidism, chromosomal or immunologic abnormalities and infectious diseases [53-55]. After ruling out the above mentioned factors, thrombophilia may be the underlying pathology in women with recurrent miscarriages [54, 55]. Adverse pregnancy outcomes reportedly associated with thrombophilia are preeclampsia, abruptio placentae, IUGR-intrauterine growth restriction, IUFD-intrauterine fetal demise and stillbirth [56]. There is debate as to whether MTHFR mutations are associated with pregnancy complications and data are inconsistent. Placental vasculopathy, seemingly determined by hyperhomocysteinemia, has been proposed as ethiopathogenic mechanism [57]. The term encompasses the abnormal placental findings at anatomopathological examination and develop

as a result of endothelial dysfunction, vasoconstriction, hypercoagulability and thrombosis, placental ischaemia and infarction, all leading to impaired placental perfusion and compromising the materno-fetal circulation [58-61]. Our patient has a history of three pregnancy losses, including stillbirth, without any identified cause except for MTHFR gene mutation causing hyperhomocysteinemia and prothrombotic state, which was not reversed by anticoagulant therapy during pregnancy.

Conclusions

The particularity of the presented case is the occurrence of two simultaneous thromboembolic events, coronary and cerebrovascular, in the presence of moderate hyperhomocysteinemia most likely due to MTHFR gene mutation. This adds to the evidence pleading for significant association of hyperhomocysteinemia with prothrombotic state leading to increased cardiovascular risk. MTHFR gene mutations, as the main causes of moderate high levels of homocysteine, should be suspected in patients with thromboembolic events and no classical risk factors. Recurrent pregnancy loss is another manifestation of thrombophilia caused by hyperhomocysteinemia and MTHFR gene mutations. Correct and timely diagnosis of thrombophilia in patients with a first embolic event or pregnancy loss, followed by adequate therapeutic management could result in improved prognosis for this category of patients.

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