HYPERHOMOCYSTEINEMIA AND TYPE II PROTEIN S
DEFICIENCY - CAUSES OF MULTIPLE ARTERIAL
THROMBOSIS

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INTRODUCTION

Even if the knowledge about the etiology of acquired or inherited thrombotic disorders have evolved a lot in the past years, mainly by elucidating the molecular mechanisms involved in the coagulation and fibrinolysis processes, the Virchow triade, postulated over 150 years ago, regarding the risk factors for thrombotic disorders (abnormalities of the blood flow, blood constituents and the vessel wall) is still valid. Today the investigation of a patient with single or recurrent episodes of unique or multiple thromboses implies a thorough search of acquired or inherited thrombogenous risk factors. The common coagulation tests are not sufficient anymore in order to explain a thrombotic syndrome.

We present the case of a 48 years old female with inherited thrombophilia (hyperhomocysteinemia and type II protein S deficiency) which evolved with multiple arterial thromboses.

CASE REPORT

M.A., 48 years old, no births in the personal history, was admitted in our hospital because of a two month history of upper abdominal pain, persistent or intermittent, sometimes colicky, not connected with food intake or time of the day, nausea, liquid vomiting or with partial digested food particles, passage of flatus, constipation and weight loss (five kilograms in two months).
Past medical history: a year before this admittance she had the symptoms of an acute surgical abdomen which proved to be bowel infarction and she underwent surgery with the resection of 45 centimeters of the small intestine. The histopathology exam: infarction of the entire resected segment and multiple thrombi in the small mesenteric vessels.

Physical exam at admission shows pain while palpating the abdomen, more intense in left upper abdominal quadrant and left flank; bowel sounds were present and there were no vascular murmurs on the main arteries. The peripheral arterial pulses were normal.

The clinical interpretation was suboclusive syndrome (Konig) possible due to postoperatory obstruction or adherential syndrome.

Laboratory findings were: inflammatory syndrome, with elevated sedimentation rate and alpha 2 globulins (60/95 mm/h and 18% respectively), leucocytosis of 11500/mm³, normal values for total cholesterol, plasma triglycerides and HDL-cholesterol.

Upper gastrointestinal tract was investigated endoscopically, which revealed an axial hiatal hernia with stage II esophagitis. Small-bowel enema (enteroelosis) revealed a 20 centimeter segment of small intestine which remained un-distained by the contrast substance and was probably secondary to a chronic, stenotic process. (Fig. 1)

Anticoagulants and vasodilators rapidly and significantly improved the symptomatology, without the need an invasive desobstruating intervention.

Abdominal arteries arteriography (Fig. 3,4) and of the lower limbs arteries performed only two weeks after the event (due to technical reasons), confirmed the occlusion of the popliteal artery (Fig. 5) and the inferior mesenteric artery, without significant proof of atherosclerotic lesions (plaques), while the superior mesenteric artery was permeable. Three days after arteriography the patient developed another episode of mesenteric infarction, although under anticoagulant therapy. This time, 70 centimeters of necrotic jejunum was resected. Post surgical evolution was unfavorable, so the next day a new surgical intervention was necessary, and this time 45 centimeters of necrotic jejunum was resected, at a distance from the previous intervention. Intraoperatory the thromboses of the small mesenteric arteries was established; no lesions at the inspection of the colon were found. The histopathological exam excluded the vasculitis aspects on the resected segment, showing only the thrombosis of the small mesenteric arteries. (Fig. 6) All the common coagulation tests performed were normal (platelets count, Quick time, partial activated thromboplastine time, antithrombin III, antiphospholipid antibodies); so we had to go further with the investigation for the coagulating and the fibrinolitic processes. Factor V resistance to activated protein C, factor VIII activity, plasma folic
Figure 3. Abdominal angiography. Inferior mesenteric artery is complete thrombosed. There are no atherosclerotic injuries and all the other abdominal vessel are normal.

Figure 4. Normal aspect of bilateral iliac arteries on angiography.

Figure 5. Right leg angiography. Complete occlusion of right popliteal artery (arrow), without collateral vessels (acute occlusion).

Figure 6. Histopathology from the latest intestinal infarction. Small vessels are thrombosed.

The final diagnosis was: **Type II protein S deficiency. Hyperhomocysteinemia. Wild type MTHFR C677T genotype.**

The patient continued with the anticoagulation therapy: first heparin, followed by warfarin, in association with aspirin, folate and vitamin B6 and B12 supplements. Further determination of homocysteine levels was not possible, but clinical evolution was good, without any thrombotic events in the next two years of surveillance.

**DISCUSSIONS**

The term of thrombophilia or prothrombotic status refers to the cases where acquired or inherited coagulation disorders enhance the susceptibility of developing venous and/or arterial thromboses. 1,2 Multiple factors causing thrombophilia can determine thrombosis in both arterial and venous territory, but according to the etiological factor there is a predominance of either of them. 2-4 (Table 1) Facing an arterial and/or venous thrombotic disorder, the acquired risk factors are the first and the easiest to analyze and identify. In a recurrent thrombotic disorder or when there are other features of thrombotic predisposition (young age and/or unusual sites of thrombosis), further investigation of the coagulation process is needed.

Recurrent arterial thrombosis in our patient, at a young age (48 years old), without any signs of atherosclerosis on vascular Doppler ultrasound and angiography, leads to a complete investigation of all inherited and acquired risk factors to explain these episodes. As hyperhomocysteinemia is frequently reported in association with thrombotic events, that was the first risk factor we looked for. 5-7 Homocysteine acid and plasma vitamin B12 level were all in normal ranges. The study of prothrombin 20210 gene variant and of MTHFR (methylenepterahydrofolate reductase) C677T gene polymorphism showed the presence of wild type. Plasma homocysteine level was elevated – 18.33 µmol/l (risk limit under 12.5 µmol/l), protein S activity was 44% (normal values between 65 and 140%), with normal free protein S antigen level.
is a sulfur-containing amino acid formed during the metabolism of methionine. Metabolism of homocysteine occurs along two major enzymatic pathways, either remethylation or transsulfuration, which require folate and vitamin B12 or vitamin B6 respectively. High plasma homocysteine levels occur in mutations in one of the enzymes involved in homocysteine metabolism. In homozygous patients the elevation is important (over 50 µmol/l) with high risk for myocardic infarction and high morbidity and mortality associated with thromboembolism, stroke, and arterial peripheral thrombosis. Also, increased plasma homocysteine levels may occur if there is not an adequate supply of vitamin B12, folate, or in chronic renal failure cases. These cases are more frequent in adults and produce only mild increases in homocysteine levels.

Despite the etiology of the mild or moderate hyperhomocysteinemia (genetic mutation with homozygous or heterozygous forms or nutritional defects), this increase is considered to be an independent risk factor for stroke, ischemic heart disease and peripheral artery disease. Chanarin (cited by ref. 8) showed that for every increase with 5 µmol/l of homocysteine levels the relative risk for coronary heart disease increases with 40%. The prospective studies of recurrent cardiovascular events showed that the hazard ratio for a recurrent event increases by 16% with each increase of 5 µmol/l in the serum homocysteine concentration. Also, lowering homocysteine concentrations with folate supplements by 3 µmol/l from current levels reduces the risk of ischemic heart disease by 16%, of deep vein thrombosis by 25%, and of stroke by 24%. There is evidence in vitro and in vivo that homocysteine is an atherogenic determinant that promotes oxidative stress, inflammation, thrombosis, endothelial dysfunction, and cell proliferation. In fact, the effects of elevated homocysteine levels appear to affect both vascular wall structure, and blood coagulation system.

Due to the moderate elevation of the homocysteine level and the absence of the atherosclerotic lesions on Doppler and angiographic examination, in our case we considered an associated risk factor explaining the amount and the extent of the thrombotic lesions. A second risk factor which could have explained the thrombotic predisposition in this patient with mild hyperhomocysteinemia was identified as type II protein S deficiency (inherited, so pre-existent to hyperhomocysteinemia).

Protein S it is a vitamin K dependent glycoprotein which acts as a cofactor for protein C to inactivate factors Va and VIIIa. In plasma, protein S has two circulating forms: 60% as a covalent complex with β-chain of the complement component C4b binding protein, while the remaining 40% is free. There are three types of protein deficiency: type I characterized by low total and free protein S antigen level; type II characterized by normal free protein S level, but reduced activated protein C cofactor activity and type III, by a selective reduction in free protein S levels. Protein S deficiency is a well known risk factor for venous thrombosis, with a 2.4 higher risk for such events including less common sites, like mesenteric or cerebral veins. Occasionally, arterial thrombosis can be found. In our case, Doppler ultrasound revealed thrombosis of the superior mesenteric artery which

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### Table 1. Acquired and inherited factors associated with arterial and venous thrombosis.

<table>
<thead>
<tr>
<th>Acquired factors</th>
<th>Arterial thrombosis</th>
<th>Venous thrombosis</th>
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<tbody>
<tr>
<td>Atherosclerosis</td>
<td>Prolonged immobilization</td>
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<tr>
<td>Diabetes mellitus</td>
<td>Trauma</td>
<td></td>
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<tr>
<td>Tobacco smoking</td>
<td>Surgery</td>
<td></td>
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<tr>
<td>Oral contraceptives</td>
<td>Pregnancy, postpartum</td>
<td></td>
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<tr>
<td>Polythemia</td>
<td>Oral contraceptives</td>
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<tr>
<td>Thrombocythosis</td>
<td>Neoplasia</td>
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<td>Paroxysmal nocturnal hemoglobinuria</td>
<td>Cancer chemotherapy</td>
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<tr>
<td>Sickle cell anemia</td>
<td>Antiphospholipid syndrome</td>
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<tr>
<td>Heparin induced thrombocythosis</td>
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<tr>
<td>Antiphospholipid syndrome</td>
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<tr>
<th>Inherited disorders</th>
<th>Arterial thrombosis</th>
<th>Venous thrombosis</th>
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</thead>
<tbody>
<tr>
<td>Hyperhomocysteinemia</td>
<td>Antithrombin, protein C, protein S deficiency</td>
<td></td>
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<tr>
<td>High Lp(a)</td>
<td>Factor V resistance to activated protein C</td>
<td></td>
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<tr>
<td>Prothrombin G20210A mutation</td>
<td>Prothrombin G20210A mutation</td>
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<tr>
<td>Protein S deficiency</td>
<td>Plasminogen deficiency, t-PA decrease or PAI-1 increase</td>
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</tr>
</tbody>
</table>

APC-activated protein C; PAI-1 – plasminogen activator inhibitor 1; t-PA tissue plasminogen activator; Lp(a) – lipoprotein a.
was not confirmed on arteriography. This could be explained by the lysis of the thrombus after the heparin therapy was initiated, while angiography was performed 2 weeks later. Even though the anticoagulant therapy was administered in proper dosage, it was not efficient on the small branches of superior mesenteric artery as the two successive intestinal infarctions followed. This comes as an argument for the multiple mechanisms involved in thrombus formation in our patient. It is also of interest that the colon was normal on macroscopic examination during surgery, in spite of the fact that the branches of the superior mesenteric artery and further more, the main branch of the inferior mesenteric artery were occluded. The occlusion of inferior mesenteric artery could have been a gradual one, so the collateral vessels could have formed and supplied the involved territory.

The involvement of hyperhomocysteinemia as a risk factor for thrombosis in this patient is obvious from the response to the treatment. Two intestinal infarctions had occurred while treated with heparin; but when given vitamin supplements (vitamin B6 and vitamin B12) and folate there were no recurrences during the two year period in which we followed her. Unfortunately it was not possible to repeat the measurement of the homocysteine levels during the vitamin treatment but, based on clinical evolution, we can only assume that the levels returned to normal values.

Even though recent studies are questioning the importance of routine measurement of plasma levels of homocysteine and that of treatment with vitamin supplements and folate in order to prevent atherothrombotic diseases, these measures proved to be beneficial in our case.15

This case is of great interest due to the association between two factors: one of them inherited (protein S deficiency) and the other one acquired (mild hyperhomocysteinemia). The pro-thrombotic activity of the first factor became clinically evident in the presence of the second one. It is possible that if any of the two risk factors were independent, they couldn't have generated such a significant thrombotic process.

REFERENCES