Original Paper

Hyperhomocysteinemia in Pregnancy and the Type of Anesthesia

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ABSTRACT: Hyperhomocysteinemia is due to genetic and acquired changes in the metabolism of homocysteine. During pregnancy, women with MTHFR genetic disorders and hyperhomocysteinemia present a high risk of thromboses; therefore they undergo antepartum anticoagulant treatment with low molecular weight heparin. Complications of pregnancy related to thrombosis and the fact that birth, as far as time is concerned, is unpredictable, lead to unique challenges when it comes to choosing the type of anesthesia. In this article we intend to discuss what type of anesthesia is suitable for patients with hyperhomocysteinemia diagnosed.

KEY WORDS: *thrombophilia, pregnancy, regional anesthesia*

Introduction

Homocysteine, an amino acid that contains a thiol group, is formed by the intracellular demethylation of methionine. In plasma, homocysteine is mainly bound to proteins, but there are also free forms, which are oxidized and disulphide.

The level of plasma homocysteine varies in relation to its 2 pathways of metabolization. The first is the trans-sulphuration to cysteine, with the help of cystathionine beta-synthase (CBS), the enzyme that requires vitamin B6 as a cofactor. The second is remethylation to methionine, which requires the presence of some enzymes (methylenetetrahydrofolate reductase MTHFR and methionine synthase), which have folic acid as a cosubstrate and vitamin B12 as coenzyme. Thus, the level of homocysteine in the blood is inversely proportional to the plasma level of folates, vitamin B12 and pyridoxal 5-phosphate (vitamin B6) and, implicitly, to the exogenous input of such vitamins (23).

The rise in the homocysteine levels is the result of an inadequate diet that is poor in folic acid and B12 or B6 vitamins and hereditary disorders of the methionine-homocysteine metabolization pathway (polymorphism of the C677T and A1298C MTHFR gene). (9, 21).

Hyperhomocysteinemia was pointed out as a risk factor for many diseases such as: HBP (18), venous thromboses, spontaneous abortions (8, 30), congenital malformations (27) and vascular dementia (2, 10).

Hyperhomocysteinemia is frequently associated with venous thromboses; therefore, the metabolism of homocysteine is investigated together with other hereditary or acquired conditions of thrombophilia. (18). Specialized literature underlines a close connection to protein C, protein S or antithrombin deficiency (24).

Hyperhomocysteinemia (a plasma level > 12-15 μmol/L) appears when one of the two metabolization pathways is blocked. Severe hyperhomocysteinemia that leads to homocystinuria is the result of genetic disorders; the most frequent is the homozygous CBS (cystathionine beta-synthase) deficiency, with an incidence of 1 to 300 000 births. These patients present mental retardation, arterial thromboembolism and they develop precocious atherosclerosis. The same type of manifestations is present in the case of homozygous MTHFR deficiency. The homozygous CBS deficiency encountered in 1% of the population is associated with moderate hyperhomocysteinemia, just as the homozygous MTHFR deficiency. Another mutation is described at the level of the MTHFR enzyme, which causes a thermolabile enzyme variant. Patients that are heterozygous for this mutation do not present hyperhomocysteinemia or an elevated risk of thrombotic events, while patients that are homozygous can develop hyperhomocysteinemia. (28). Other causes of hyperhomocysteinemia include: folate and vitamin B6 deficiency, older age, hypothyroidism, systemic lupus erythematosus, chronic kidney diseases, drugs: nicotinic acid, methotrexate, teophylline, L-dopa.

Recently, high levels of homocysteine and the homozygous state for the C677T mutation at the level of the MTHFR gene (which causes a thermolabile enzyme variant that is 20% less efficient in the metabolization of homocysteine)

have been associated with certain pregnancy complications that include: chromosomal anomalies, congenital malformations, recurrent miscarriages, placental disorders and preeclampsia.

Moreover, aside from the consequences on the embryo or fetus in the first stages of the pregnancy, the two factors are also involved in thromboembolic events occurring late in the pregnancy or even in the post-partum period. (29).

In fact, thrombophilia in a pregnant woman is correlated to the emergence of a complication. The pregnancy status is characterized by physiological hypercoagulation caused by an increase in most coagulation factors (I, II, VII, VIII, IX, X) and a decrease in fibrinolytic anticoagulant factors, changes that are basically produced on a hormonal basis (1).

The association between thrombophilia and pregnancy creates a special anesthetic moment, because thrombophilia predisposes to hypercoagulation and requires anticoagulant treatment to prevent thromboembolism, a treatment that needs to be administered continuously. In emergency situations, the anesthesiologist needs to make a decision regarding the choice of the right anesthetic for the solving of the case. Regional anesthesia techniques are relatively contraindicated in a patient that receives preventive or curative anticoagulant treatment, because of the risk of spinal hematoma. However, in literature the cases of post-regional anesthesia hematoma are rather few (1/150.000–250.000), therefore there is the possibility that the risk has been overrated. General anesthesia, through the use of nitrogen protoxide, inhibits the conversion of homocysteine into methionine, thus increasing the risk of thrombosis in the post-anesthesia period (3, 4).

Materials and methods

I have done a study in which I tried to find the most efficient anesthetic method for patients with homocysteinemia. The study was made on 98 patients with thrombophilia, women in the last trimester of pregnancy. They undergo anticoagulant treatment since the diagnosis of thrombophilia was discovered. During the pregnancy, the patients also received group B vitamin supplements and folic acid 5 mg/day. In 71 patients I have performed rachianesthesia with a 26-27G pencil point needle, L_3-L_4 level, 0.5% bupivacaine. In 10 patients the birth finished vaginally under peridural anesthesia with 18G Tuohy needle, L_4-L_5 level, 0.2% ropivacaine + sufentanil; 17 patients received general anesthesia. Homocysteine was drawn up for all patients in the group before and after the operation, and the evolution of the homocysteine levels was monitored in relation to the type of anesthesia.

Results

I have made a statistic average of the levels of homocysteine before and after the operation. There was an increase in the level of homocysteine in post-op in patients that received general anesthesia with nitrogen protoxide.(fig.1.) We should take into consideration that the patients are under treatment with folic acid and B group vitamins. Therefore, the general anesthesia with nitrogen protoxide predisposes to risks of thrombosis by increasing the levels of homocysteine.

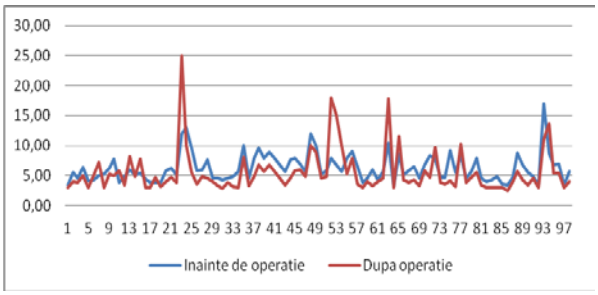

Fig.1. Levels of homocysteine in pre- and post-op

Discussion

Hyperhomocysteinemia has a prevalence of almost 5-16% of the general population (15). Since hyperhomocysteinemia is a known risk factor for arterial and venous thromboses, as well as for precocious abortions, it is recommended to normalize the homocysteine level through adequate vitamin substitution, the same way is was done in this case once the diagnostic of homozygous A1298C and C677T mutation thrombophilia and hyperhomocysteinemia was established; the conventional treatment for hyperhomocysteinemia included B group vitamin supplements: folic acid, B6, B12 and anticoagulant treatment to prevent vascular thromboses (14).

Genetic anomalies of methylenetetrahydrofolate reductase (MTHFR) affect the synthesis of N5-methylenetetrahydrofolate (MTHF). Genetic disorders of MTHFR cause important increases in homocysteine levels (100 micromoles/l); however, compared to B6 and B12 vitamin deficiency, MTHFR anomalies are much less frequent. A reduction in the levels and activity of MTHFR induces hyperhomocysteinemia, which represent a risk factor for thrombotic events (20). The group

of patients was also tested for A1298C and C677T mutations.

Studies in literature show that the A1298C form is associated with hyperhomocysteinemia and low levels of folic acid. Plasma levels higher than 10 micromoles/l are associated with a doubling of the vascular risk. The increase of the risk of thrombosis results from the atherogenic activity of homocysteine which increases the procoagulant activity of the plasma. Plasma level higher than 12 micromoles/l must be treated aggressively with folic acid and B group vitamins (26).

Hyperhomocysteinemia caused by MTHFR gene mutations or folate deficiency is associated with major complications of the pregnancy in the 3rd trimester (preeclampsia, uteroplacental apoplexy, separation of the normally inserted placenta), because hyperhomocysteinemia acts on the surface of the endothelial cells, causing intervillous thromboses and impairment of placental perfusion (13).

The problem was raised whether thrombophilia is involved or not in obstetrical complications; some studies argued that there is no association, but most studies showed that thrombophilia is involved especially in recurrent abortion, preeclampsia and intrauterine growth restriction (7, 12, 25).

The involvement of hyperhomocysteinemia in the production of thrombotic events also recommends anticoagulant treatment throughout the pregnancy, which raises problems in the choice of anesthesia when the Cesarean section is indicated fetal extraction (4).

The American Society for Regional Anesthesia and Pain Medicine has established, at the second Consensus of the Regional Anesthesia and Pain Medicine Conference in 2002, that subcutaneous mini-doses for thromboprophylaxis with unfractionated heparins does not constitute a contraindication for the use of anesthetic techniques at the level of the rachidian channel. However, the number of thrombocytes must be evaluated before administering the rachianesthesia and the catheter should be removed in patients that have received standard unfractionated heparin for more than 4 days. In patients that receive oral anticoagulants for long periods of time, the anticoagulant treatment should be stopped at least 4-5 days before the planned procedure, and the aPTT/INR levels should be measured before performing any maneuver at the level of the rachidian channel. Another recommendation of the ASRA Consensus Conference was that in patients who are administered LMWH (low-molecular-weight heparin) in pre-op for thromboprophylaxis, the anesthetic maneuver at the level of the rachidian channel should be done at least 10 to 12 hours after the last LMWH dose (11, 17).

The safest solution would be general anesthesia, but one that does not involve the use of nitrogen protoxide (6). Nitrogen protoxide oxidizes the cobalt atom of vitamin B12, inactivating the methionine-synthase and determining a dose-dependent increase of the plasma concentrations of homocysteine 4 days after the surgery. The acute increase of the plasma concentrations of homocysteine affects the endothelial function, induces oxidative stress and potentially destabilizes the endothelium of the coronary arteries. Moreover, a number of studies have reported an increase in myocardial ischemia within the first 48 hours and the production of some cardiovascular events within the first 30 days in patients that had received nitrogen protoxide anesthesia (16, 22).

Nitrogen protoxide promotes the procoagulant activity, increases thrombocyte adhesivity, affects the endothelial function and the V factor, inhibits the C protein and III antithrombin. Severe neurological impairments of the child subjected to nitrogen protoxide general anesthesia have been ascertained and reported.

Conclusions

Anticoagulant and antithrombotic therapy is more and more indicated for the thromboprophylaxis and treatment of thrombotic complications during the pregnancy, as well as for the prophylaxis of high-risk pregnancy loss; one of these high-risk pregnancies is the pregnancy associated with thrombophilia. Many antithrombotic and anticoagulant agents are available nowadays. New anticoagulants are emerging and the clinical applications in pregnant patients continue to evolve and represent unique challenges for the anesthesiologist.

Although anesthesia societies in many countries have developed assistance guides and protocols for anesthesiologists, there are many uncertainties regarding the optimal moment for the rachianesthesia, especially in the case of pregnant women that undergo anticoagulant therapy.

The decision to use rachianesthesia, epidural anesthesia or general anesthesia in parturients that are subject to such medication should be individualized and based on a careful evaluation of the risk-benefit ratio.

Regional anesthesia can be done in safe conditions if the anticoagulant therapy is interrupted 8-12 hours before the surgery and if the values of thrombocytes, aPTT and INR, as well as the activated factor X activity (heparinemia), are within normal limits.

General anesthesia that involves the exposure of such patients to nitrogen protoxide should be avoided.

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