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General anesthesia and methylenetetrahydrofolate reductase deficiency

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Abstract
Methylenetetrahydrofolate reductase (MTHFR) deficiency is an autosomal recessive disorder with a spectrum of manifestations including neurological symptoms, premature arteriosclerosis, and venous and arterial thrombosis. Most patients are heterozygous for multiple MTHFR substitutions; small minorities are homozygous for mutations at this locus. Among these mutations, the C677T polymorphism is the most deleterious. Nitrous oxide use in anesthesia leads to significant increases in plasma homocysteine. We present a patient undergoing urgent surgery with a preoperative diagnosis of homozygous MTHFR deficiency.

Key words Nitrous oxide · Homocysteine · Methylenetetrahydrofolate reductase deficiency

Introduction

Methylenetetrahydrofolate reductase (MTHFR) deficiency is an autosomal recessive disorder that results in increased homocysteine levels in the body [1]. Nitrous oxide (N_2O) inhibits methionine synthetase, which transforms homocysteine to methionine, which result in increased homocysteine levels [2]. Hyperhomocysteinemia itself predisposes to venous and arterial thrombosis with a sixfold increased risk compared to the normal population [3]. Therefore, it is important to avoid N_2O while administering anesthesia to patients with MTHFR deficiency.

Case report

A 44-year-old woman, American Society of Anesthesiology (ASA) physical status II, 68 kg, 158 cm, Mallampati class 3 airway, presented with cellulitis of the right foot. The patient had a homozygous *MTHFR* gene mutation diagnosed within the previous year, which predisposed her to vascular thrombosis. Of note, the patient was found to be a homozygote for the MTHFR C677T mutation by polymerase chain reaction and restriction endonuclease digest. Anticoagulation with coumadin was initiated after diagnosis; however, she was admitted to our institution 6 months later with acute gastrointestinal bleeding and an INR of 14.1. The patient was administered two units of fresh frozen plasma (FFP) and two units of packed red blood cells with resolution of gastrointestinal bleeding; however, the patient's serum creatinine became elevated to 3.1 mg/dl and the diagnosis of renal artery thrombosis was made. The patient was discharged with coumadin anticoagulation and an INR of 3.5 and was not seen by a healthcare provider until her current presentation to the emergency room with cellulitis of the right foot.

Upon arrival to the emergency department her INR was 5.8 and thrombin time (PT) was 58.3 s. Additional laboratory results revealed; WBC 25.8 k·μl^{-1}, RBC 3.29 MIL·μl^{-1}, hemoglobin 8.5 g/dl, hematocrit 26%, and a platelet count of 268 k·μl^{-1}. The patient stated that she had stepped on a screw, which lodged in the right third toe, the screw had been removed, with subsequent worsening cellulitis. Physical examination revealed a right third toe which had turned gangrenous at the puncture site. The patient was admitted to the hospital and started on antibiotics and a heparin infusion to maintain anticoagulation and was scheduled for amputation of the gangrenous toe. Her admission medications included coumadin 80 mg in the morning and 80 mg in the evening, and folic acid 1 mg twice a day. The patient was hemodynamically stable. Because the patient was given anticoagulation therapy, it was decided that general anesthesia would be administered the following morning for amputation of the gangrenous toe. Prior to the surgery, two units of FFP were

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administered; within 30 min of this administration severe bronchospasm occurred and the patient was brought emergently to the operating room (OR). Of note, the preoperative INR was 4.2. The patient underwent general anesthesia with a balanced technique using desflurane and rocuronium; N_2O was not used. After successful surgical intervention, the patient's INR was 3.8 and coumadin was restarted. On the first postoperative day the patient experienced shortness of breath, and subsequent chest X-ray revealed bilateral pneumonia. Anticoagulation was continued and her subsequent INR was 4.5. The patient continued to deteriorate and was subsequently mechanically ventilated and transferred to the intensive care unit (ICU), where the patient developed chest pain and hypotension to 80 mmHg systolic. A 12-lead electrocardiogram showed nonspecific ST-T changes and inverted T waves in leads V_1 to V_3. Cardiac enzymes were elevated; her hypotension was managed by normosol infusion at a rate of 150 ml·h^{-1} and a transfusion of 2 U of packed red blood cells. Coumadin was stopped and she was started on continuous heparin infusion for 48 h and then switched to enoxaparin sodium. After 1 week of hospitalization, the patient developed acute renal failure, requiring hemodialysis, secondary to severe renal artery thrombosis. On postoperative day (POD) 7, the patient's respiratory status remained critical and tracheostomy was performed without major sequelae. On POD 10, the patient's condition began to improve as the pneumonia began to resolve and her anticoagulation was adequately maintained on enoxaparin sodium. Respiratory status continued to improve and the patient was transferred from the ICU to the general surgical ward on POD 17. The patient, however, remained in renal failure with renal replacement therapy. The patient was discharged from the hospital on POD 39. Prior to hospital discharge the patient was converted from enoxaparin sodium to coumadin for anticoagulation therapy. At the time of hospital discharge her INR was 3.5 and PT was 43.6 s. Additional laboratory results revealed; serum creatinine 3.5 mg·dl^{-1}, WBC 8.4 k·µl^{-1}, RBC 3.62 MIL·µl^{-1}, hemoglobin 10.5 g/dl, hematocrit 32%, and a platelet count of 235 k·µl^{-1}. The patient continued on hemodialysis as an outpatient and her discharge medications included coumadin 2 mg twice a day and folic acid.

Discussion

Methylenetetrahydrofolate reductase (MTHFR) deficiency is an autosomal recessive disorder with a spectrum of manifestations including neurological symptoms, premature atherosclerosis, and venous and arterial thrombosis. A total of 29 mutations in MTHFR are associated with severe deficiency, with a resulting activity level that is usually 0% to 30% of control activity [4]. Most patients are heterozygous for multiple MTHFR substitutions; a small minority is homozygous for mutations at this locus. Among these mutations, the C677T polymorphism is the most important. Our patient in this report was homozygous for this polymorphism.

The prevalence of hyperhomocysteinemia in the general population is not known. In European, Middle Eastern, and Japanese populations, the prevalence of the heterozygous thermolabile variant mutation in MTHFR is 30% to 40%, and the homozygous mutation is 10% to 15% [5]. However, in African Americans the prevalence of either mutation is less than 5%, and homozygosity in indigenous Mexicans approaches 35% [6].

Partial deficiencies (i.e., heterozygous for multiple MTHFR substitutions) have been observed in otherwise normal subjects who have premature vasoocclusive disorders [3]. Vitamin supplements are effective in reducing plasma homocysteine levels in these subjects; however, vitamin supplementation with anticoagulation therapy is usually required to prevent vasoocclusive disorders in patients, such as ours, that are homozygous for the MTHFR C677T mutation [5]. In addition to the increased risk of thrombotic complications to the cardiovascular system, the renal system is particularly vulnerable to thrombosis in patients homozygous for the MTHFR C677T mutation [5]. Our patient developed renal artery thrombosis and significant reduction of renal function, thereby diminishing her drug-clearance ability in this critical setting.

The mechanism of hyperhomocysteine leading to vascular disorders is poorly understood. However, animal studies have demonstrated that higher plasma total homocysteine levels are linked to both enhanced platelet aggregation and thromboxane synthesis [7]. Dose-response studies with thrombin and adenosine diphosphate (ADP)-evoked platelet aggregation have demonstrated a causal relationship with concurrent rises in plasma homocysteine [8]. These increases in platelet aggregation may be influenced by an excessive production of oxygenated reactive species. Indeed, animal studies have demonstrated significant increases in circulating oxidation products (such as lipoperoxides) following methionine load, which were associated with enhanced platelet aggregation, all of which were ameliorated by the administration of the antioxidant probucol [9]. Theoretically, this enhanced platelet aggregation and increase in oxidation products associated with hyperhomocysteinemia could have contributed to our patient's renal failure (perhaps through microvascular thrombus [10]) and bronchospasm (through increase in oxidative products and release of histamine [11]).

Agents such as acetylsalicylic acid (aspirin)], for its antiplatelet effects, and n-acetylcysteine, for its antioxidant effects, could be studied in settings of hyperhomocysteinemia to try and prevent morbidities such as occurred in our patient.

In regard to the perioperative care of these patients, we suggest that, preoperatively, the patient's coagulation status should be corrected prior to surgery by FFP infusion. This reduction of the elevated PT is very temporary. Resuming anticoagulation should be done immediately after operation, because the patient is at high risk of vascular thrombosis or embolization. Other suggestions include establishing adequate hydration, and hemodynamic stability.

Intraoperatively, nitrous oxide (N_2O) should not be used, specifically in patients who are homozygous for the MTHFR C677T mutation [12,13]. N_2O inhibits methionine synthetase, resulting in the reduction of the conversion of homocysteine to methionine, thus increasing systemic homocysteine levels [14]. Acute increases in systemic homocysteine via the use of N_2O have been linked to endothelial dysfunction [15] and a procoagulant state potentially mediating pathologic consequences [16]. Nevertheless, N_2O-based anesthesia continues to be used due to its low cost, potent analgesic effects, and its rapid onset and elimination.

The mechanisms for N_2O-induced increases in homocysteine are complex. N_2O directly inhibits methionine synthetase irreversibly, thus slowing the conversion of homocysteine to methionine and increasing homocysteine concentrations, with the de-novo synthesis of the enzyme required to restore activity [17]. The mean half-life of inactivation is 46 min. Residual methionine synthetase activity more than 200 min after the start of N_2O administration approaches zero [18]. Therefore, N_2O anesthesia leads to significant increases in plasma homocysteine, which has been confirmed by several clinical studies [2,13,19].

Badner et al. [13] randomized 20 patients to receive general anesthesia with or without N_2O (inspired >50%). Plasma homocysteine increased 100% in those patients receiving N_2O and these levels were sustained for 24 h following surgery, while plasma levels in control patients were unchanged. This study, however, was too small to determine the clinical significance of this change. Therefore, the same group of investigators [2] randomized 90 patients in a similar fashion to examine the effects of N_2O anesthesia-induced elevation of plasma homocysteine and myocardial ischemia. These investigators found a twofold increase in the incidence of myocardial ischemia in those receiving N_2O. Furthermore, a significant association was found between peak postoperative homocysteine levels greater than 17 $\mu mol \cdot l^{-1}$ and myocardial ischemia, with a relative risk of 2.0 ($P < 0.05$) [2].

Postoperatively, patients with MTHFR deficiency should resume anticoagulation as soon as possible. Delaying this treatment may contribute to major thrombotic complications within the brain, heart, or kidney. It is also important to keep the patient adequately hydrated, and to avoid bradycardia, hypoxemia, and hypothermia in order to avoid the effects of increased blood viscosity or vascular spasm that may contribute to clot formation.

In addition, it has been suggested that moderate hyperhomocysteinemia in any person or family merits further evaluation in the preoperative period. Although many cases of hyperhomocysteinemia may be due to nutritional factors (i.e., low folate intake) recent evidence suggests that the modern inclusion of folic acid into vitamin supplements and enriched foods is reducing the frequency of nutritionally based hyperhomocysteinemia, thereby increasing the relevance of such testing in suggesting an underlying abnormality predisposing these patients' adverse outcomes [3]. However, there are conflicting data [20]. Therefore, several questions remain for the anesthesiologist. Should all patients with very high preoperative homocysteine levels be tested for MTHFR deficiency? If not, then should N_2O be avoided in all patients with very high preoperative levels, and if so what is this level of homocysteine that would merit this avoidance? These questions merit further clinical investigation.

Conclusion

We have presented a case of methylenetetrahydrofolate reductase (MTHFR) deficiency in a patient undergoing urgent surgery. We discussed anesthesia management for this type of patient preoperatively, intraoperatively, and postoperatively. It is recommended that N_2O be avoided in patients with MTHFR deficiency undergoing general anesthesia. If the patient's liver function is within normal limits, total intravenous anesthesia should be considered. Neuroaxial or regional anesthesia can be considered, but should be avoided in those patients on anticoagulant therapy. To prevent emboli and/or thrombosis, the patients with MTHFR deficiency should be sufficiently anticoagulated whenever possible during their hospitalization and in the community. Kidney damage secondary to emboli or thrombosis is more common than other organ damage in patients presenting with this deficiency. Therefore, drug clearance is of significant concern for patients with MTHFR deficiency, and these patients should be closely monitored postoperatively for the occurrence of myocardial infarction and pulmonary emboli.

References

1. Jakubowski H (2006) Pathophysiological consequences of homocysteine excess. J Nutr 136:1741S–1749S
2. Badner NH, Beattie WS, Freeman D, Spence JD (2000) Nitrous oxide-induced increased homocysteine concentrations are associated with increased postoperative myocardial ischemia in patients undergoing carotid endarterectomy. Anesth Analg 91:1073–1079
3. Ueland PM, Nygard O, Vollset SE, Refsum H (2001) The Hordaland Homocysteine Studies. Lipids 36(Suppl): S33–S39
4. Kniffin CL (2002) 5,10-Methylenetetrahydrofolate reductase; MTHFR. OMIM
5. Refsum H, Nurk E, Smith AD, Ueland PM, Gjesdal CG, Bjelland I, Tverdal A, Tell GS, Nygard O, Vollset SE (2006) The Hordaland Homocysteine Study: a community-based study of homocysteine, its determinants, and associations with disease. J Nutr 136:1731S–1740S
6. Ganji V, Kafai MR (2004) Serum total homocysteine concentration determinants in non-Hispanic White, non-Hispanic Black, and Mexican-American populations of the United States. Ethn Dis 14:476–482
7. Di Minno G, Davi G, Margaglione M, Cirillo F, Grandone E, Ciabattoni G, Catalano I, Strisciuglio P, Andria G, Patrono C (1993) Abnormally high thromboxane biosynthesis in homozygous homocysteinuria. Evidence for platelet involvement and probucol-sensitive mechanism. J Clin Invest 92:1400–1406
8. Harpel PC, Zhang X, Borth W (1996) Homocysteine and hemostasis: pathogenic mechanisms predisposing to thrombosis. J Nutr 126:1285S–1289S
9. Durand P, Lussier-Cacan S, Blache D (1997) Acute methionine load-induced hyperhomocysteinemia enhances platelet aggregation, thromboxane biosynthesis, and macrophage-derived tissue factor activity in rats. FASEB J 11:1157–1168
10. Bahloul M, Dammak H, Kallel H, Khlaf-Bouaziz N, Ben Hamida C, Chaari A, Chelly H, Rekik N, Bouaziz M (2007) Thrombotic microangiopathies. Incidence, pathogenesis, diagnosis, treatment and prognosis (in French). J Mal Vasc 32:75–82
11. Geronikaki AA, Gavalas AM (2006) Antioxidants and inflammatory disease: synthetic and natural antioxidants with anti-inflammatory activity. Comb Chem High Throughput Screen 9:425–442
12. Gerges FJ, Dalal AR, Robelen GT, Cooper B, Bayer LA (2006) Anesthesia for cesarean section in a patient with placenta previa and methylenetetrahydrofolate reductase deficiency. J Clin Anesth 18:455–459
13. Badner NH, Freeman D, Spence JD (2001) Preoperative oral B vitamins prevent nitrous oxide-induced postoperative plasma homocysteine increases. Anesth Analg 93:1507–1510
14. Christensen B, Refsum H, Garras A, Ueland PM (1992) Homocysteine remethylation during nitrous oxide exposure of cells cultured in media containing various concentrations of folates. J Pharmacol Exp Ther 261:1096–1105
15. Chambers JC, McGregor A, Jean-Marie J, Kooner JS (1998) Acute hyperhomocysteinaemia and endothelial dysfunction. Lancet 351:36–37
16. Mayer EL, Jacobsen DW, Robinson K (1996) Homocysteine and coronary atherosclerosis. J Am Coll Cardiol 27:517–527
17. Frasca V, Riazzi BS, Matthews RG (1986) In vitro inactivation of methionine synthase by nitrous oxide. J Biol Chem 261: 15823–15826
18. Guttormsen AB, Refsum H, Ueland PM (1994) The interaction between nitrous oxide and cobalamin. Biochemical effects and clinical consequences. Acta Anaesthesiol Scand 38:753–756
19. Lacassie HJ, Nazar C, Yonish B, Sandoval P, Muir HA, Mellado P (2006) Reversible nitrous oxide myelopathy and a polymorphism in the gene encoding 5,10-methylenetetrahydrofolate reductase. Br J Anaesth 96:222–225
20. Hansrani M, Oates C, Stansby G (2006) A prospective patient observational study of the role of hyperhomocysteinemia in restenosis in patients undergoing infrainguinal angioplasty or bypass procedures. Int Angiol 25:378–384