



Methylene Tetrahydrofolate Reductase Deficiency: the Hidden Risk in Paediatric Anaesthesia

Metilen Tetrahidrofolat Redüktaz Eksikliği: Pediatrik Anestezide Gizli Risk

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Objective: Methylene tetrahydrofolate reductase (MTHFR) deficiency is an autosomal recessive disorder that results in increased homocysteine levels in the body. Hyperhomocysteinemia causes a predisposition to venous and arterial thrombosis and ischaemic insults. The incidence of the deficiency is around 40% in some countries. In this study, we aimed to evaluate the effects of anaesthetic agents in children with MTHFR deficiency.

Methods: Twelve paediatric patients with an MTHFR enzyme deficiency who underwent surgery in a ten-month period in a single centre were retrospectively evaluated. Demographic data, homocysteine levels before and after surgery, anaesthesia management and postoperative complications were recorded.

Results: In four patients, propofol was used both for anaesthesia induction and total intravenous anaesthesia (TIVA). Eight patients received sevoflurane for both induction and maintenance of anaesthesia. Nitrous oxide (N₂O) was not used in any patients. There was not a significant difference between the preoperative and postoperative homocysteine levels ($p>0.05$). Twenty-four hours after the surgery, the homocysteine levels were within normal limits. No complications were observed.

Conclusion: Sevoflurane and propofol have no deleterious effects on homocysteine levels in patients with MTHFR deficiency. Avoidance of N₂O is the key point for anaesthetic consideration regarding these patients.

Keywords: Methylene tetrahydrofolate reductase deficiency, homocysteine, nitrous oxide, children

Amaç: Metilen hidrofolat redüktaz (MTHFR) eksikliği vücutta artmış homosistein seviyeleri ile sonuçlanan otozomal resesif bir bozukluktur. Hiperhomosisteinemi venöz ve arteriyel tromboza zemin hazırlar ve iskemik olaylara neden olur. İnsidans bazı ülkelerde %40'a kadar çıkar. Bu çalışmada MTHFR eksikliği olan çocuklarda anestezi ajanlarının etkisini değerlendirmeyi ve konuyu meslektaşlarımıza hatırlatmayı amaçladık.

Yöntemler: Tek merkezde, on aylık bir periyoda cerrahi uygulanan ve MTHFR enzim eksikliği bulunan on iki hasta retrospektif olarak değerlendirildi. Demografik veriler, cerrahi öncesi ve sonrası homosistein seviyeleri, anestezi uygulaması ve postoperatif komplikasyonlar kaydedildi.

Bulgular: Dört hastada hem anestezi indüksiyonu hem de total intravenöz anestezi (TIVA) için propofol kullanıldı. Sekiz hasta anestezi indüksiyonu ve idamesi için sevofluran aldı. Hiçbir hastada azot protoksit (N₂O) kullanılmadı. Preoperatif ve postoperatif homosistein seviyeleri arasında anlamlı fark yoktu ($p>0.05$). Operasyondan yirmi dört saat sonra homosistein seviyeleri normal sınırlar içindeydi. Herhangi bir komplikasyon gözlenmedi.

Sonuç: MTHFR eksikliği olan hastaların homosistein seviyeleri üzerine sevofluran ve propofolün zararlı etkisi yoktur. Bu hastaların anestezisinde azot protoksitten kaçınılması anahtar noktadır.

Anahtar Kelimeler: Metilen tetrahidrofolat redüktaz eksikliği, homosistein, nitroz oksid, çocuk

Introduction

Methylene tetrahydrofolate reductase (MTHFR) deficiency is an autosomal recessive disorder that results in increased homocysteine levels in the body. Manifestations of the disease are neurological symptoms (progressive hypotonia, convulsions and physicomotor retardation), premature atherosclerosis and venous and arterial thrombosis. Hyperhomocysteinemia predisposes patients to venous and arterial thrombosis with a three to six-fold increased risk compared to the normal population (1, 2).

Methylene tetrahydrofolate reductase deficiency bears significance in terms of anaesthesiology. In North America, every year approximately 45 million people undergo anaesthesia, and in about half of them, N₂O is used as a major component of the

anaesthesia because of its short onset and elimination time, potent analgesic and amnesic properties and low cost. N₂O inhibits methionine synthetase, which transforms homocysteine to methionine and leads to an increase in homocysteine levels in the body (3). The common use of N₂O increases the possibility of exposure for patients with MTHFR deficiency to N₂O. There is not a report about the effects of anaesthetic agents other than N₂O on these patients.

The aim of the study was to investigate the effects of the anaesthetic agents on children with an MTHFR deficiency and to briefly review the subject.

Methods

The study was conducted under ethical principles from the Declaration of Helsinki and national laws.

The hospital records of the paediatric patients with an MTHFR deficiency who underwent surgery over a 10-month period (April 2014–February 2015) in our clinic were evaluated retrospectively. Written informed consent was routinely obtained before intervention from the caregivers. This included consent for sharing medical data for future medical publications. A written consent from the hospital administration was obtained before gathering data from the patient logs and hospital records for this retrospective review.

The age and gender of the patient, presenting signs and symptoms, current medication, type of MTHFR gene mutation, type of operation, anaesthesia management, post anaesthetic care unit (PACU) time, clotting disorder, preoperative and postoperative homocysteine values and postoperative complications were recorded.

Statistical analysis

The results were analysed using the student-t test. All data were presented as the mean ± standard deviation. A p value of less than 0.05 was considered significant.

Results

There were 2344 children operated on under general anaesthesia for various reasons between April 2014 and February 2015. Among these, 12 had a diagnosis of MTHFR deficiency. There were 7 males and 5 females (Table 1). The mean age was 3.5±2.7 (3.5 months–9 years) years. The MTHFR gene mutation was diagnosed during investigations for generalised convulsions in four, for hypotonia in two and for nystagmus, retinitis pigmentosa and growth retardation in one each. In the remaining three, screening was done because of a positive family history. The primary care physician was a paediatric metabolism specialist. They all regularly used Vitamin B12 and folate. Preoperative PT, aPTT, %PT and INR levels as well as homocysteine levels were within normal limits (Table 1). The mean preoperative homocysteine level was 5.36±1.98 µmol L⁻¹. During the perioperative period, all were monitored by standard means, namely, electrocardiogram, non-invasive blood pressure, end-tidal anaesthetic and CO₂ monitoring and pulse oximetry. In the four patients whom intravenous access was carried out before entering the operating room, both the induction of anaesthesia and the total intravenous anaesthesia (TIVA) maintenance was achieved using a propofol, oxygen (O₂) and air mixture. The remaining eight patients who did not have intravenous lines received sevoflurane and O₂ and air both for induction and maintenance of anaesthesia. Why TIVA or inhalation anaes-

Table 1. Characteristics of the patients with an MTHFR deficiency

Case	Gender	Age (years)	Operation	Presenting symptoms/signs	MTHFR gene mutation	Anaesthesia type	Preoperative homocysteine (µmol L ⁻¹)	Postoperative homocysteine (µmol L ⁻¹)
1	Male	2	Hypospadias correction	Convulsion	C677T	TIVA	6.37	5.99
2	Male	2	Inguinal hernia repair	Family history	C677T	TIVA	2.38	3.17
3	Female	9	Cystoscopy	Nystagmus	A1298C	TIVA	6.40	5.91
4	Female	7	Nissen fundoplication	Convulsion	C677T	TIVA	1.45	1.61
5	Female	3	Adeno-tonsillectomy	Family history	C677T	Sevoflurane	4.50	5.82
6	Male	7	Inguinal hernia repair	Family history	C677T	Sevoflurane	5.42	4.70
7	Female	1	Inguinal hernia repair	Retinitis pigmentosa	A1298C	Sevoflurane	5.30	4.38
8	Male	2	Orchiopexy	Growth retardation	C677T	Sevoflurane	6.15	5.38
9	Male	3	Adenoidectomy	Hypotonia	C677T	Sevoflurane	5.48	4.41
10	Male	3	Orchiopexy	Convulsion	C677T	Sevoflurane	5.42	3.46
11	Female	0.3	Cataract surgery	Hypotonia	A1298C	Sevoflurane	9.20	8.37
12	Male	3	Laparotomy for hepatic cyst	Convulsion	C677T	Sevoflurane	6.27	1.76

TIVA: total intravenous anaesthesia

thetia methods were preferred in different patients was only based on the existence of the intravenous line. N₂O was not used in any of the patients.

Seven children were intubated using rocuronium. In the others, a laryngeal mask was placed for management of the airway. At the end of the operations, the patients were extubated after an injection of atropine 0.15 mg kg⁻¹ and neostigmine 0.3 mg kg⁻¹. Postoperative analgesia was provided with paracetamol 20 mg kg⁻¹ intravenously. The PACU time was approximately one hour for all patients. When the modified Aldrete score reached 9, the patients were transferred to their beds. Blood samples were obtained for homocysteine analysis 24 hours after the anaesthesia (Table 1). The mean postoperative homocysteine level was 4.58±1.91 µmol L⁻¹ with no statistically significant difference between the pre- and postoperative values ($p>0.05$). The mean postoperative homocysteine level was 4.17±2.15 µmol L⁻¹ in those who underwent TIVA, and the same value was 4.79±1.9 µmol L⁻¹ in those managed by sevoflurane. There were not complications with any patients.

Discussion

Polymorphisms in the MTHFR gene have been reported as possible risk factors for a variety of common conditions. These include heart disease, stroke, hypertension, high blood pressure during pregnancy (preeclampsia), glaucoma, psychiatric disorders, certain types of cancer and a group of birth defects that occur during the development of the brain and spinal cord (neural tube defects) (4).

The prevalence of the MTHFR deficiency in the general population is unknown in Turkey. In European, Middle Eastern and Japanese populations, the prevalence of the heterozygous mutation in MTHFR is 30%–40%, and the homozygous mutation is 10% to 15% (2). Our patients had a definitive genetic diagnosis of MTHFR deficiency and were transferred from other hospitals because of the probable intensive care unit (ICU) necessity in the postoperative period. In fact, none of these patients did not require the ICU postoperatively. The most important point in the postoperative period is close monitoring of the patients.

Methylene tetrahydrofolate reductase plays a key role in folate metabolism and in the homeostasis of homocysteine; mutations in the enzyme lead to hyperhomocysteinemia (4). N₂O inhibits methionine synthetase, which transforms homocysteine to methionine and leads to an increase in homocysteine levels in the body (1). These mechanisms lead to higher homocysteine levels in MTHFR deficiency patients who receive N₂O.

Many factors lead to a rise in the homocysteine levels, some of them are vitamin B12, folic acid and vitamin B6 deficiencies, diabetes, thyroid dysfunction, oestrogen deficiency rheumatoid arthritis, some long term medications, including corticosteroids, chronic inflammatory diseases, some intesti-

nal disorders, such as coeliac and Crohn's diseases, inadequate diet, high coffee and alcohol intake, some prescription drugs (such as proton pump inhibitors) and smoking. Levels increase with age and are commonly higher in men than women. All children in the presented series had genetic confirmation of the MTHFR deficiency.

Homocysteine acts as an atherogenic and thrombophilic agent. An acute increase in plasma homocysteine is associated with impaired endothelial function. It produces direct cytotoxic effects on endothelial cells and causes procoagulant activity, which includes increased platelet adhesiveness, factor V activation, protein C inhibition and antithrombin and plasminogen activator binding (5).

Because of the common use of N₂O, the probability of patients with MTHFR deficiency being exposed to N₂O increases. Therefore, it is essential to avoid N₂O use in patients with the MTHFR deficiency during anaesthesia management. Moreover, it is noteworthy that N₂O may lead to an increase in homocysteine levels in normal patients who do not have an MTHFR deficiency (6). On the other hand, N₂O used in anaesthesia for patients with the MTHFR deficiency causes more deleterious effects than in normal patients. In a study, Selzer et al. (7) investigated the cause of the neurologic deterioration and death of a child anaesthetised twice with N₂O before the diagnosis of an MTHFR deficiency. The patient was a 3-month old ASA I male who had an infantile fibrosarcoma in the left leg. Anaesthesia was maintained with 0.75% halothane and 60% N₂O in oxygen in two consecutive surgeries. He was discharged on the seventh postoperative day after the second excisional surgery. Twenty-five days after the resection, the patient returned to the hospital because of seizures and episodes of apnoea. He was severely hypotonic, without reflexes and with ataxic ventilation. Laboratory tests revealed that the urine was positive for homocysteine, and the plasma homocystine level was elevated. Forty-six days after the resection, he died. After genetic investigations, the patient was diagnosed with an MTHFR deficiency. Thus, they concluded that the N₂O induced methionine synthase defect superimposed on an inherited defect of MTHFR caused the patient's death (7). Based on this result, in the patients diagnosed with MTHFR deficiency, N₂O should not be used during anaesthesia management. In the case of emergency procedures, in patients whose clinical presentation fits MTHFR deficiency, even if the disorder is not a diagnosis, N₂O should not be used. In elective procedures, patients whose clinical presentation fits MTHFR deficiency should be evaluated, and the diagnosis should be ruled out before N₂O is used. Familial history must be questioned during the preoperative evaluation.

There is no consensus about the upper reference limits for plasma homocysteine concentrations. In healthy individuals, the 'normal' concentrations commonly range from 5 to 15 µmol L⁻¹. However, according to some studies, the upper limit of 15 µmol L⁻¹ is too high in populations without an obvious

vitamin deficiency. It was proven that each increase of 5 $\mu\text{mol L}^{-1}$ in the homocysteine level increases the risk of coronary heart disease events by approximately 20%, independent of traditional coronary heart disease risk factors. In addition, it was determined that homocysteine concentrations between 10 and 15 $\mu\text{mol L}^{-1}$ are the basis of the risk for coronary artery disease. Some reports indicate that homocysteine measurements over 6.3 $\mu\text{mol L}^{-1}$ represent an increased risk (8).

Homocysteine levels must be under 7 $\mu\text{mol L}^{-1}$ for patients with an MTHFR deficiency in the preoperative period to minimise complications. However, one of our patients had a 9.20 $\mu\text{mol L}^{-1}$ homocysteine value; the peri- and postoperative course was uneventful in that single patient.

Both heterozygote and/or homozygote mutations in the gene for homocysteine metabolism may confer an increased risk for premature vascular disease and arterial thrombosis by causing hyperhomocysteinemia (9, 10). The determining factor seems to be the homocysteine level of each individual patient.

In some cases, even though N_2O was not used, ischaemic insults might develop. A patient undergoing urgent surgery with a preoperative diagnosis of homozygous MTHFR deficiency was reported. The patient was using coumadin and folic acid for prevention of ischaemic insults. She had cellulitis of the right foot, and the right third toe had turned gangrenous. General anaesthesia with a balanced technique using desflurane and rocuronium was administered for amputation of the gangrenous toe. N_2O was not used during the operation. Despite these measures, she had a coronary ischaemic insult and renal artery thrombosis in the postoperative period. The authors concluded that such patients should be closely followed postoperatively for the occurrence of myocardial infarction and pulmonary emboli even though N_2O was not used in anaesthesia management (2).

Anticoagulation therapy is schemed according to general rules before surgery in patients with MTHFR deficiency. The patients should restart anticoagulation therapy as soon as possible in the postoperative period. Delaying this treatment may contribute to major thrombotic complications within the kidney, heart or brain. It is also important to keep the patient adequately hydrated, and to avoid hypoxaemia, hypothermia and bradycardia, in order to avoid the effects of increased blood viscosity or vascular spasms that may contribute to clot formation.

Badner et al. (11) designed a study to determine whether oral B vitamins, which are cofactors in homocysteine metabolism, can prevent N_2O -anaesthesia-induced homocysteine increases in patients undergoing elective surgery. They concluded that preoperative B vitamins inhibit N_2O induced increases in plasma homocysteine concentrations that occur after surgery (11).

All our patients were under Vitamin B_{12} and folate treatment, and they were followed up regularly. Their homocysteine levels were in normal limits before the surgery, most likely

because they were under regular medication. N_2O was not used in their anaesthesia management, and the postoperative homocysteine levels remained unchanged. No complications were observed in any patients in the postoperative period.

Conclusion

The common use of N_2O should be reviewed because of the existence undiagnosed patients with an MTHFR deficiency in society. The patients with an MTHFR deficiency should be followed up closely in the postoperative period regardless of whether or not N_2O was used due to the susceptibility of the patients for ischaemic insults. Sevoflurane and TIVA can be used safely in patients with an MTHFR deficiency.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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