CASE REPORT

A case of homocystinuria: anesthetic implications

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ABSTRACT

We report a case of 12 yr. old male child who presented with diminshed vision for 3-4 years and was found to have supranasal subluxation of lens. He was suspected to have homocystinuria and confirmed by high serum homocysteine level. Homocystinuria is second most common inherited amino acid metabolic disorder, associated with cystathionine-beta-synthetase deficiency. After reducing his serum homocysteine level with medication, patient was taken up for surgery under general anesthesia. During perioperative period prolonged fasting hours and use of nitrous oxide were avoided and use of pneumatic compressions was taken to avoid the various complications and mortality associated with this syndrome.

Key words: Homocystinuria; Thromoboembolism; Dehydration; Nitrous oxide

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INTRODUCTION

Classical homocystinuria due to cystathionine beta-synthase (CbS) deficiency is an autosomal recessively inherited disorder of methionine metabolism. The current cumulative detection rate of CbS deficiency is 1 in 344,000.[1] Classical homocystinuria involves four major organ system- eye, skeletal, central nervous system and cardiovascular. It can also involve liver, skin and hair. It is associated with high incidence of thromboembolic events and mortality.[2] So better understanding of this disease has led to better anesthetic outcome in these patients. We present a case of homocystinuria who presented for a surgery and anesthetic consideration in these types of cases.

CASE REPORT

A 12 yrs old child presented with a complaint of decreased vision. On examination he was found to have bilateral subluxation of lens, for which pars plana vitrectomy and lensectomy with lens implantation was planned. He was suspected to have homocystinuria and was confirmed by high serum homocysteine level.

On preanesthetic check up, history revealed full term normal vaginal delivery of child and with no perinatal complications with history of speech delay at age of 3 years. He was studying in 6th class and lagged behind in studies as compared to his colleagues. He was found to have weight of 30 kg, height of 143.5 cm and arm span of 154.5 cm. He had triangular face, hypertelorism and a high arched palate. He had long spider like fingers but with no joint hypermobility. Psychoneurological examination revealed borderline intelligence with adaptive behavioural deficit. Heart auscultation revealed a diastolic murmur in aortic area.

His routine hematological, biochemical investigations and coagulation profile were normal. ECG showed sinus rhythm with left ventricular hypertrophy. Chest x-ray and USG abdomen were also normal. Lab investigation showed;

Serum homocysteine level: 39 μmol/l (normal 5-15 μmol/l)

Total cysteine level: 760 μmol/l (normal 245-332 μmol/l)

Urine homocysteine: 21.5 mmol/mol creatinine (normal 0.2-0.4 mmol/mol creatinine)

Echo: Moderate AR with aortic root dilation,

Ejection fraction: 60-65%

MRI spine: 1.2x0.6 cm well defined T1 hypo and T2 hyperintense lesion seen in right sacral neural foramina at S1-S2 level. Rest of the spine was normal.

He was started on folic acid 5 mg tablets OD, pyridoxine 200 mg/day, inj. vitamin B12 IM OD, aspirin 75 mg OD and metoprolol 12.5 mg OD for headache by the pediatrician. He was then scheduled to undergo surgery after 4 weeks of medications.

On the day before surgery, all of his preoperative investigations including coagulation profile were normal except a low blood sugar. Serum homocysteine level had reduced to 28μmol/l. On the day of surgery, pyridoxine, folic acid, Vitamin B12, aspirin, metoprolol were given in the morning and the patient was allowed to take water till two hours before surgery. An intravenous infusion of 5% dextrose was started at 6 AM to treat low blood sugar level in morning i.e 65 mg/dl. In Operation Theatre routine monitors were attached and basal vital parameters were noted. The patient was premedicated with tablet alprazolam 0.25mg in night before surgery and induced with inj. propofol 60 mg and inj. fentanyl 30 microgram IV. Relaxation was achieved with vecuronium 3 mg and the airway secured with a cuffed ETT size 6.0 mm. Anesthesia was maintained with oxygen, isoflurane and vecuronium with controlled ventilation. Nitrous oxide was avoided. Automatic pneumatic compressions were applied to both lower limbs to prevent venous stasis. The patient was reversed with glycopyrrolate and neostigmine. The intraoperative course was uneventful. The surgery finished in 2 hours 15 mins and the postoperative period was uneventful. Intravenous infusion of 5% dextrose was given postoperatively and the patient was allowed oral intake of water after 4 hrs. The perioperative blood sugar was checked at regular interval and was found to be in normal limits. Postoperatively was monitored for any thromboembolic event. The patient was discharged 4 days after the operation.

DISCUSSION

Homocystinuria is an inherited autosomal recessive disease caused by a deficiency in cystathionine b-synthase.[1] CbS enzyme is an enzyme that converts homocysteine to cystathionine in trans sulphuration of methionine cycle. The classical amino acid profile of homocystinuria includes homocystinuria and hyperhomocysteinaemia, hypermethioninemia and low plasma cystine and cystathionine. Both methionine and homocystine accumulate in various tissues as well as in blood and urine. It is a multisystemic disorder of the connective tissue, muscles, CNS and cardiovascular systems.[2] High myopia and ectopia lentis are major ocular manifestations, indeed many cases have been diagnosed because of it. The characteristic long thin extremities and arachnodactyly usually appear during late in childhood or adolescence. Marfanoid habitus[3] is usually present in these patients. Pes excavatum, genu valgum and kyphoscoliosis are common. Osteoporosis, usually of the spine is an early manifestation and distinguished feature. Mental retardation is most common CNS abnormality of CbS deficiency.

CNS and psychomotor delay may occur during the first year of life, developmental delay (in patients aged 2-3 years), psychiatric symptoms, pyramidal symptoms including muscle weakness may occur. However thromboembolic events, such as cerebrovascular occlusions or pulmonary emboli are more common in adults than in children.[2] The risk of thromboembolism is known to increase after surgical procedures. Various mechanisms seem to operate to increase the risk of thromboembolism. These include enhancing activity of coagulation factors (V,XII), altering the antithrombotic function of endothelium by depressing the level of antithrombotic factors or endothelial derived nitric oxide, increased platelet adhesiveness, elevated blood viscosity and mean arterial pressure. Vascular occlusive disease is an important and serious feature and may result in renal infarction and cor pulmonale.[4] \Homocystinuria produces high concentrations of amino acids that are competitive inhibitors of tyrosinase which leads to decreased melanin and manifests as malar rashes and fragile hair. The screening test is the cyanide nitroprusside reaction in the urine. Diagnosis is confirmed by analysis of methionine, homocysteine, and cystathionine levels. Medical care varies according to age of diagnosis. There are currently three recognised modalities of treatment;[5]

1. Pyridoxine
2. Methionine restricted, cysteine-supplemented diets (max 500 mg/d.) Folic acid and Vit B12 are used in partial responders.
3. Betaine (3-methylglycine) is used in pyridoxine resistant patients.

Treatment response should be monitored by serial serum homocysteine level.

Anesthetic Considerations:

A) Prevention of thromboembolism:[3,5,6] Pre-operative measures include dietary measures to lower or control serum methionine and homocystine levels, adequate preoperative intravenous hydration and pharmacological measures including administration of low dose aspirin, dipyridamole and low molecular weight heparin should be done. Any drug that may predispose to a hypercoaguable state e.g. oral contraceptives should be avoided. Intraoperative measures: include: maintenance of intraoperative cardiac output, pneumatic stockings to prevent peripheral stagnation of blood, use of dextran 40 and early ambulation in postoperative period.

B) Maintenance of high cardiac output and rapid circulation time.

C) Good venous return- by adequate IV fluids and reduction of peripheral resistance.

D) Avoid use of nitrous oxide - Nitrous oxide should be avoided in the anesthetic administration as N2O causes increase in the levels of blood homocystine by inhibiting methionine synthase[7]. Nitrous oxide induced increase in homocysteine levels was also associated with an increase in postoperative myocardial ischaemia[8].

E) Prevent hypoglycemia- The mechanism of hypoglycemia[9] is that there is increased methionine leading to increased insulin release resulting in hypoglycemia. This may be prevented by reducing the period of fasting, perioperative administration of intravenous dextrose and monitoring of perioperative blood sugar levels.

F) Rapid recovery and early ambulation- use short acting and rapidly metabolizing anesthetic drugs.

CONCLUSION

In summary, homocystine, because of its effect on platelet adhesiveness, may result in serious thromboembolic phenomena, especially following general anesthesia. To minimize these risks, special attention must be paid to the avoidance of dehydration and hypovolemia, giving drugs to reduce homocysteine level preoperatively and the maintenance of good venous return in addition to the early ambulation of the patient.

These patients postoperatively should be monitored for 36 – 48 hours for any thromboembolic event. Recognition and control of this condition before surgery and judicious management after surgery could reduce the anesthetic morbidity and mortality of these patients.

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