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# Anaesthetic Management of a Young Patient with Homocystinuria

Ali Asghar and Faiza Mazhar Ali

## ABSTRACT

Homocystinuria is a rare autosomal recessive genetic disease. It is caused by a deficiency in cystathionine- $\beta$ -synthase leading to a defect in methionine metabolism. High levels of plasma homocysteine are associated with vascular injury via mechanisms of oxidative damage, vascular smooth muscle proliferation, promotion of platelet activation and aggregation, and disruption of normal procoagulant-anticoagulant balance favouring thrombosis. This is a case of 8 years old boy, a known case of homocystinuria, who was scheduled for bilateral lensectomy and intraocular lens placement. The major anaesthetic considerations include the development of thromboembolism, need to avoid nitrous oxide in balanced anaesthesia regimen and hypoglycaemia.

**Key words:** Homocystinuria. Thromboembolism. Nitrous oxide.

## INTRODUCTION

Homocystinuria is a rare autosomal recessive genetic disease.<sup>1</sup> The incidence of homocystinuria is approximately 1 in 200,000 live births.<sup>2</sup> It is due to the deficiency of the enzyme cystathionine-beta-synthase leading to accumulation of homocysteine.<sup>3</sup> It is generally classified into three types due to an enzyme deficit at three different sites associated with the metabolism of the amino acid methionine. Type-I is caused by a deficiency of the cofactor pyridoxine (vitamin B<sub>6</sub>) and the enzyme cystathionine synthase. Type-II is due to a deficiency of the enzyme tetrahydrofolate methyltransferase and type-III is from a defect of the enzyme tetrahydrofolate reductase.<sup>3</sup>

High levels of plasma homocysteine are associated with vascular injury via mechanisms of oxidative damage, vascular smooth muscle proliferation, promotion of platelet activation and aggregation, and disruption of normal procoagulant-anticoagulant balance favouring thrombosis.<sup>3</sup> Symptoms may occur as mildly delayed development or failure to thrive. Increasing visual problems may also lead to diagnosis of this condition. There is no cure for homocystinuria. The conventional treatment of hyperhomocysteinemia includes folate supplementation, usually with vitamin B<sub>6</sub> or B<sub>12</sub>. Those who do not respond will need to eat a low-methionine diet.<sup>4</sup>

Better understanding of the disease has lead to better anaesthetic prognosis in these patients.<sup>3</sup> We present here a case of homocystinuria who underwent surgery with anaesthetic management.

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## CASE REPORT

An 8 years old boy, known case of homocystinuria presented with complaint of recurrent headache and diminished vision. On ophthalmic evaluation, the child was found to have glaucoma due to bilateral ectopia lentis, therefore, he was scheduled for bilateral lensectomy and intraocular lens placement.

On pre- anaesthetic evaluation, he had a past history of sudden onset of weakness and loss of consciousness one year back. On workup, he was found to have extensive dural sinus thrombosis. At that time, he was placed on warfarin and a CT scan was done after 20 days which showed complete resolution. During that period extensive workup was done, on which he was diagnosed as a case of homocystinuria.

On examination, he weighed 25 kilograms and his height was 130 centimeters. His general physical and systemic examination including central nervous system examination were normal. The laboratory investigations were within normal limits except for high levels of serum homocysteine, which was 120 micromol/litres. In medication history, he was taking pyridoxine 50 mg BID, folic acid 5 mg BID, vitamin C 100 mg QD, multivitamin 5 mg QD, acetylsalicylic acid 75 mg QD, betaine 1.5 gm TID, hydroxocobalamin 1 gm QD and enoxaparin 25 mg BID.

On the day of surgery, an intravenous infusion of 5% dextrose was started. The patient was pre-medicated with syrup midazolam 0.25 mg/kg. After taking the patients in operating room, standard ASA monitoring (ECG, NIBP and SpO<sub>2</sub>) was applied. To prevent thromboembolism, elastic stocking and automated pneumatic foot compression system was applied. General anaesthesia was planned with control mode of ventilation. Patient was induced with intravenous propofol 2 mg/kg along with fentanyl 2 ug/kg and atracurium 0.5 mg/kg. Airway was secured with RAE tube size 6.0 mm. anaesthesia was maintained with

isoflurane 2% in 50:50 oxygen and air. Intraoperatively intravenous infusion of 5% dextrose was continued to prevent hypoglycaemia as well as blood sugar was checked which was found to be normal. The patient was reversed with atropine 0.2 mg/kg and neostigmine 0.05 mg/kg. Duration of surgery was 90 minutes. The intraoperative course as well as postoperative course of the patient was uneventful. The patient was discharged after 3 days.

## DISCUSSION

Homocystinuria is an inherited autosomal recessive disease caused by a deficiency in cystathionine- $\beta$ -synthase leading to a defect in methionine metabolism.<sup>3</sup> Plasma levels of homocysteine are controlled by two distinct metabolic pathways. Homocysteine may be salvaged to methionine by remethylation, or degraded to cysteine by trans-sulfuration.<sup>5</sup> Homocysteine may acquire a methyl group from either N-5-methyltetrahydrofolate (MTHF) or from betaine to reform methionine. Re-methylation to methionine is catalyzed by the ubiquitous enzyme, methionine synthase (MS). This enzyme uses vitamin B12 (methylcobalamin) as a co-factor, and MTHF as methyl donor. MTHF is formed from folic acid by the enzyme, 5,10-methylene tetrahydrofolate reductase (MTHFR). Homocysteine is diverted to the trans-sulfuration pathway when methionine concentrations exceed the capacity of the methionine cycle or when the synthesis of cysteine is required.<sup>5</sup> Cystathionine- $\beta$ -synthase (CBS) and vitamin B<sub>6</sub> are required for trans-sulfuration.<sup>5</sup> CBS catalyzes the union of homocysteine and serine to form cystathionine. Cystathionine is hydrolyzed to form cysteine and ketobutyrate.

Both methionine and homocysteine accumulate in various tissues as well as in blood and urine. It is a multi-systemic disorder of the connective tissue, muscles, central nervous and cardiovascular systems. Severe myopia is the first sign of ectopic lentis and may precede lens dislocation by several months to a year.

There are three major anaesthetic considerations; there are the development of thromboembolism, avoidance of nitrous oxide in balanced anaesthesia regimen and hypoglycaemia.<sup>6</sup>

Various mechanisms seem to operate to increase the risk of thromboembolism. These include enhancing activity of coagulation factors (V, XII), altering the anti-thrombotic function of endothelium by depressing the level of anti-thrombotic factors or endothelial derived nitric oxide, increased platelet adhesiveness, elevated blood viscosity and mean arterial pressure and impairment in endothelium mediated platelet inhibition.<sup>6</sup> Teng *et al.* reported a case of homocystinuria, in which the risk of thromboembolism was minimized by the administration of low-dose salicylic acid. An elastic stocking and automated pneumatic foot compression

system, which we used, can also help avoid thromboembolism.<sup>7</sup>

Nitrous oxide (N<sub>2</sub>O) should be avoided in the anaesthetic administration as N<sub>2</sub>O causes increase in the levels of blood homocysteine by inhibiting methionine synthase.<sup>8</sup> The effect of N<sub>2</sub>O anaesthesia and post-operative plasma homocysteine levels on myocardial ischaemia were evaluated in a randomized controlled trial by Badner *et al.*<sup>8</sup> Patients undergoing carotid endarterectomy were monitored for ischaemic events with a three-channel Holter monitor. The investigators found an association between elevated homocysteine levels and a significantly increased incidence and duration of postoperative ischaemia in the patients treated with N<sub>2</sub>O.<sup>9</sup> In one report, a 40 years old man with a history of hyperhomocysteinemia had a combined total N<sub>2</sub>O exposure of 11 hours during evaluation and management of right lower-limb arterial insufficiency. Four weeks after exposure to N<sub>2</sub>O, this patient exhibited severe sensorimotor deficits that were improved with vitamin B supplementation.<sup>10</sup> Selzer *et al.* recently reported neurological deterioration and death of a child anaesthetized twice with nitrous oxide, who was later diagnosed homocystinuria.<sup>2</sup>

The mechanism of hypoglycaemia is increased via methionine leading to increased insulin release resulting in hypoglycaemia.<sup>6</sup> This may be prevented by reducing the period of fasting, perioperative administration of intravenous dextrose and monitoring of perioperative blood sugar levels.

To prevent thromboembolism, enoxaparin, elastic stockings and intermittent foot compression with a pneumatic system were used. Careful perioperative management should be used for this kind of rare metabolic disorder to prevent serious anaesthetic problems.

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