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Anesthetic implications of homocystinuria: A case report

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Abstract

Introduction: Homocystinuria is an inherited metabolic disorder associated with cystathionine beta-synthase deficiency leading to accumulation of both methionine and homocysteine in various connective tissues and blood manifesting clinically as multisystem disorder. It is associated with a high incidence of thromboembolic complications and high mortality during the perioperative period. Homocystinuria imposed number of anesthetic challenges during the perioperative period.

Case Report: A 10-year-old male presented with dimness of vision and was found to have ectopia lentis. Based on his clinical findings, he was suspected to have homocystinuria. This was confirmed by his high serum homocysteine levels. The child was posted for lensectomy with vitrectomy. The homocysteine and methionine level were brought down to the safer limit by month-long medical and nutritional therapy before taking up for the surgery. The surgery was done under general anesthesia and peribulbar block. The perioperative measure included avoidance of prolonged fasting, avoidance of nitrous oxide, mechanical and chemical thromboprophylaxis, and early mobilization. The patient had an uneventful post-operative period.

Conclusion: Understanding the perioperative hazards and complications of homocystinuria can be avoided with proper preparation of the patient, judicious use of anesthetic techniques. This case report described some of the anesthetic challenges during management of such a patient.

Keywords: Homocystinuria, general anesthesia, thromboembolism, nitrous oxide.

Introduction

Homocystinuria is an inborn error of transsulfuration metabolic pathway due to cystathionine-β-synthase deficiency. It is biochemically characterized by increased plasma homocysteine, methionine, and decreased cysteine [1,2]. Clinically, it manifests as multisystemic connective tissue disorder involving mainly muscles, central nervous, and cardiovascular systems. It is associated with a high incidence of thromboembolic complications and high mortality [3, 4]. Homocystinuria imposes a number of perioperative challenges notably the hypercoagulability and thromboembolic events, hypoglycemia, airway, and position-related problem and management of anticoagulants, etc. In recent years, understanding of the pathophysiology and treatment of homocystinuria has improved, which helped in early diagnosis and long-term survival. As a result, the number of patients needing surgical correction of deformity associated with homocystinuria or surgical or coexisting disease is on the rise. We encountered a child with homocystinuria suffering from ectopic lentis for lensectomy with vitrectomy. The aim of reporting the case is to highlight and discuss the perioperative management and particularly the anesthetic implications of such rare clinical condition.

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Case Report

A 10-year-old male child weighing 20 kg presented to the ophthalmology outpatient department with sudden onset redness of eye associated with dimness of vision, vomiting, and headache. He had similar complaints in the past. He had chronic papillary block angle closure glaucoma with ectopia lentis (Fig. 1) and lens-induced cyclitic. Family history positive for consanguineous marriage, but there was no history of similar complaints in the family. On examination, he was found to have marfanoid features (arm span more than the height), pectus excavatum, dysmorphic facies, and high-arched palate (Fig. 2-4). He had a subnormal intelligence but was a cheerful and cooperative. Examinations of all the systems were within normal limits. Routine hematology including coagulation parameter and biochemistry was within normal limit. Electrocardiogram showed a few atrial ectopics, but echocardiogram was essentially normal. Serum homocysteine levels were >65 mmol/l (normal values are 3–14 mmol/l). Urine spot nitroprusside test was positive. All the other investigations were found to be within normal limits. Hence, he was diagnosed as a case of homocystinuria with ectopia lentis.

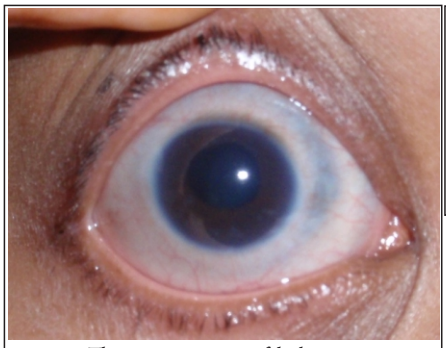

Figure 1: The ectopic position of the lens.

Figure 2: Marfanoid limb.

Figure 3: High-arched palate.

He was started on oral Vitamin B6, B12, and folic acid along with oral aspirin 50 mg once daily and enoxaparin (low-molecular-weight heparin) 18 mg subcutaneous twice daily for thromboprophylaxis. He was also started on acetazolamide 125 mg thrice daily by an ophthalmologist to reduce the intraocular pressure. Diet therapy included restriction of methionine intake and addition of cysteine supplementation. After 4 weeks of medical treatment, the homocysteine levels came down to 30 mmol/l. He was posted for lensectomy with vitrectomy. To avoid dehydration, he was encouraged to have clear fluids till 2 h before surgery. Aspirin and enoxaparin were hold on the day of surgery. The child was admitted on the day of surgery. After admission, an intravenous infusion of dextrose 5% with half normal saline was started at 80 ml/h. No premedication was administered in the ward. Child was shifted to operative room. Before shifting to operating table (OT), on the pre-operative holding area, child was given midazolam 1 mg along with 20 mcg of fentanyl. Once child was shifted to OT table, routine monitors were attached. Mechanical thromboprophylaxis (pneumatic compression device) applied on both lower limbs. Child was induced with propofol 50 mg along with inhalation of sevoflurane at 3%; no 2.5 classic laryngeal mask airway (LMA) was inserted once the child was sufficiently deep plane of anesthesia. Maintenance of anesthesia was done with sevoflurane 2–3% dial setting and child was left to breathe on its own, through pediatric breathing circuit. After induction of general anesthesia, ophthalmic surgeon gave peribulbar block with a combination of 2% lignocaine 3 ml and 0.5% bupivacaine 3 ml. Intraoperative course was uneventful, the surgery lasted for 30 min. After completion of surgery, the LMA was removed. O2 was administered through a facemask and child shifted toward after 30 min observation in recovery room. Intravenous fluid was continued into post-operative period till the oral intake was adequate. He was mobilized as soon as possible. He was restarted on prophylaxis against thrombosis after 6 h of surgery. Oral fluids were started within 2 h. The post-operative period was uneventful. The patient was discharged on the 2nd post-operative day.

Figure 4: Pectus excavatum.

Discussion

Clinical manifestations during infancy are non-specific and may include failure to thrive and developmental delay. The diagnosis is usually made after 3 years of age, when subluxation of the ocular lens (ectopia lentis) occurs. Affected individuals with homocystinuria manifest skeletal abnormalities resembling those of Marfan syndrome; they are usually tall and thin, with elongated limbs, and arachnodactyly. Scoliosis, pectus excavatum or carinum, genu valgum, pes cavus, high-arched palate, and crowding of teeth are commonly seen. These children usually have fair complexions, blue eyes, and peculiar malar flush. Generalized osteoporosis, especially of the spine, is the main X-ray finding. Thromboembolic episodes involving both large and small vessels, especially those of the brain, are common and may occur at any age. Optic atrophy, paralysis, cor pulmonale, and severe hypertension (due to renal infarct) are among the serious consequences of thromboembolism. The risk of thromboembolism increases during perioperative period. Spontaneous pneumothorax and acute pancreatitis are other rare complications. Elevations of both methionine and homocystine or (homocysteine) in body fluids are the diagnostic laboratory findings [4]. Treatment with high doses of Vitamin B6, B12, and folic acid causes dramatic improvement in most patients who are responsive to this therapy. Patients should not be considered unresponsive to Vitamin B6 until folic acid (1–5 mcg/24 h) has been added to the treatment regime. Restriction of methionine intake and cysteine supplementation is recommended. Administration of large doses of Vitamin C has improved the endothelial function; long-term clinical efficacy is not known. Some of the anesthetic implications are as follows [1, 4, 5, 6, 7]:

1. High risk of development of thromboembolism and arteriopathy
2. Nitrous oxide exposure induced sudden increase the homocysteine level
3. Risk of development of hypoglycemia
4. Intubation problems and chest deformity may lead to ventilatory difficulties
5. Associated rare complications such as pneumothorax, hypertension, cor pulmonale, and osteoporosis
6. Presence of fragile bone and limb and trunk deformity-positioning problem

Increased in homocysteine level is associated with higher risk of vasculopathy, particularly the coronary and cerebral vessels leading to acute myocardial ischemia and strokes. The mechanism for accelerated vasculopathy in homocystinuria is not fully understood, suggested mechanisms are endothelial cell damage, proliferation of vascular smooth muscle cells, lipid peroxidation, imbalance in prothrombotic, and antithrombotic factors[6,7,8]. In

addition to risk of myocardial ischemia and strokes, patients with homocystinuria are particularly prone for thromboembolic events in perioperative and post-operative periods. Episodes of thromboembolism are common following general anesthesia even with minor surgeries[4]. This is thought to be due to the stress response generated by general anesthesia. Hence, regional anesthesia should be the alternative. However, any nerve block performed close to large or intermediate vessels could initiate vascular damage resulting in thromboembolic phenomenon[7]. Thromboembolism can be reduced by adequate pre-operative intravenous hydration, administration of low dose aspirin, and low-molecular-weight heparin. Any drug that may predispose to a hypercoagulable state should be avoided. Intraoperative measures include maintenance of intraoperative cardiac output, pneumatic stockings to prevent peripheral stagnation of blood, use of dextran, and early ambulation in the post-operative period[1,7]. Peribulbar block when used as an adjunct to general anesthesia was a safe and useful analgesic technique for pediatric ophthalmic surgery[9,10]. Although peribulbar block with general anesthesia is considered safe, surgery under peribulbar block alone can still raise concern about the ability of the children to cooperate. Although most cases of ophthalmic surgeries for homocystinuria reported in the literature were done under general anesthesia, there have been two cases where regional anesthesia was used [10,11,12]. However, these were adults with normal intelligence. Our child was 10 years old and was cooperative for the surgery; the child-parent wishes to have general anesthesia during the surgery to avoid any mental trauma on the child that may lead to post-traumatic stress disorder. Nitrous oxide should be avoided in patients with homocystinuria avoided as it inhibits methionine synthetase slowing the conversion of homocysteine to methionine and further increasing the homocystine level[13]. Acute increase in homocysteine level causes endothelial dysfunction and has procoagulant effects and has been reported as risk factor for post-operative myocardial ischemia [14]. The procoagulant effects include increased platelet adhesiveness, factor V activation, protein C inhibition, antithrombin, and plasminogen activator binding. These actions are probably mediated by consumption of nitric oxide and/or production of hydrogen peroxide. The mechanism of hypoglycemia is due to increase in methionine level which stimulates the pancreatic cell to release more insulin. Hypoglycemia may be prevented by restricting pre-operative fasting to the acceptable minimum, administration of intravenous dextrose, and monitoring perioperative blood glucose[1]. We opted for safe outcome of the patient, it was an elective case, so medical management was started to reduce the serum homocysteine level lower value along with systemic anticoagulation and antiplatelet therapy to reduce the perioperative thromboembolic events. Avoided prolonged fasting and encourage oral sugar containing fluid up to 2 h before surgery. Avoidance of nitrous oxide, combining regional technique with general anesthesia helps us to avoid long-acting opioid. Although there was relatively little risk of hematoma formation after the peribulbar block, we had stopped the low-molecular-weight heparin for more than 24 h and instructed ophthalmologist to use very fine needle for the block placement. Intraoperative mechanical thromboprophylaxis in the form of pneumatic pump as thromboprophylaxis which was continued postoperatively. Due to combining regional block with general anesthesia (GA), the stress of the surgery was reduced, we could keep child in little lighter plane of anesthesia and help him in early recovery and ambulation. Surgery could have been done only under GA, but with sole GA the stress level and recovery would have been longer which might have other negative implication such as post-operative nausea vomiting, delay ambulation, and greater risk of thromboembolism.

Avoidance of GA at all will have been better choice, but since the child was relatively small and at such age undergoing surgery solely under block would have been more traumatic to the child, we respected the parent wished and proceeded with GA combined with peribulbar block.

Limitation: Since this is a single case report, it will be difficult to make a generalized comment, and each case has to be dealt with individualized approach depending on the patient characteristic, nature, and urgency of the surgery.

Conclusion

Understanding the perioperative hazards and complications of homocystinuria can be avoided. Pre-operative medical management to reduce blood homocysteine level is extremely important to reduce the risk of perioperative thromboembolism in addition to perioperative thromboprophylaxis, avoidance of dehydration/hypovolemia, hypoglycemia, and use of nitrous oxide.

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