Byler's disease and anesthetic consideration

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SUMMARY: Dal D, Salman E, Başgül E. Byler's disease and anesthetic consideration. Turk J Pediatr 2003; 45: 74-77.

Byler's disease is an autosomal recessive condition characterized by intrahepatic cholestasis, progressive fibrotic changes and finally cirrhosis that leads to death during childhood. This is a report of a six-year-old girl with Byler's disease and retrobulbar hematoma as a result of trauma who underwent enucleation and implantation. This case report describes the anesthetic features of a patient with Byler's disease in which anesthetic agents with no or minimal hepatotoxic effect should be used to avoid deterioration of liver function.

Key words: Byler's disease, familial intrahepatic cholestasis, general anesthesia.

Byler's disease is one of the familial intrahepatic cholestasis syndromes[1]. This autosomal recessive disease is characterized by intrahepatic cholestasis and progressive changes to fibrosis and finally terminal cirrhosis leading to death before adulthood[2]. It is the second most common form of familial intrahepatic cholestasis. The disease usually presents in infancy, and is restricted to the liver without any other organ involvement except for extrahepatic manifestations of cholestasis including rickets from vitamin D malabsorption and vitamin E deficiency-associated neurological syndrome, including areflexia, gait disturbances and retinal pigmentary changes. Patients are usually mentally retarded; faces are not as typical as in Allagile's syndrome but can be defined as "coarse"[2]. They have a family history of consanguinity or an affected sibling. They present usually with jaundice, pruritus or hepatomegaly at 6-12 months and splenomegaly may accompany. Laboratory tests usually demonstrate cholestasis with elevated serum bile acids, alkaline phosphates and bilirubin with normal cholesterol level. Transaminases (gamma-glutamyl transferase and 5 nucleotidase) and lipoprotein X are normal or elevated moderately. Pathologically, biopsy can be normal[1] or giant cell hepatitis or minimal paucity of intrahepatic bile ducts can be found. Also periportal or intralobular fibrosis without true nodule formation can be seen. Cholestasis eventually becomes persistent and leads to hepatic failure with ascites, encephalopathy and finally death.

Pathogenesis is based on a defect in hepatic metabolism, perhaps a defect in transport, formation or excretion of primary blie acids. At the present time, only treatment is orthotopic liver transplantation.

Case Report

A six-year-old girl with a weight of 15 kilograms was referred to the hospital with the diagnosis of retrobulbar hematoma as a result of head trauma. She was born at term, the first pregnancy of a 24-year-old healthy mother, with low birth weight. Her seven-month old twin died from pneumonia. The parents were first-degree cousins. She had a 2.5-year-old healthy sister. Byler's disease was diagnosed at 2.5 years. She was under medical treatment for hepatic precoma with acetazolamide (3x10 mg) and with amikacin and ceftriaxone for her undercurrent infections during her referral to the ophthalmology department. In her physical examination her left eye was ecchyomatic (Fig. 1). Ascites, hepatomegaly 5 cm from the edge of the costa at the midclavicular line and splenomegaly 3-4 cm from the edge of the costa at the midclavicular line were present. Hepatic function tests were abnormal. In abdominal ultrasound, cholestasis and gallstones with a few millimeters in diameter were observed. In her liver biopsy, increment in the pericellular

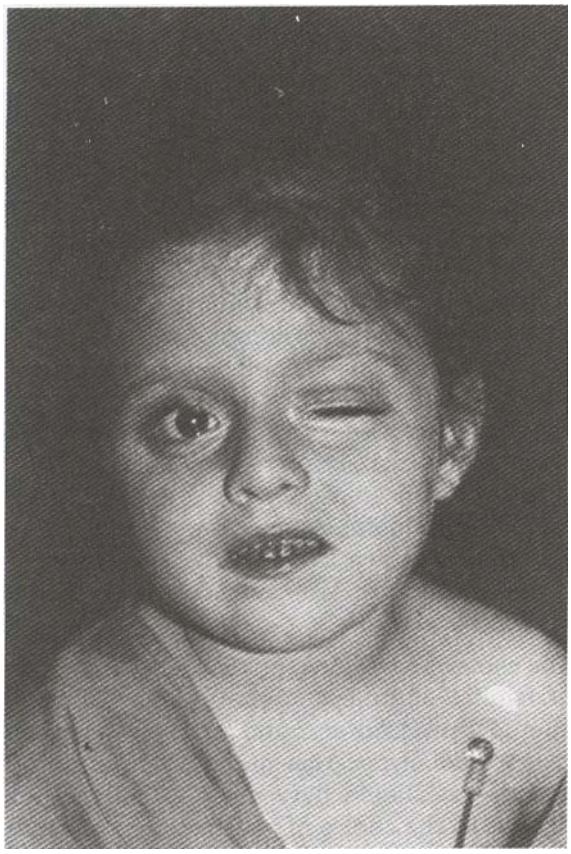

Fig. 1. Ecchymotic eye of the patient.

collagen tissue and copper binding protein deposits were seen in the periseptal hepatocytes. Cirrhotic process was observed with partial ductopenia. In cranial computerized tomography (CT), a hyperdense lesion resembling a left retrobulbar hemorrhage was reported. Left orbital mass was reported in cranial magnetic resonance imaging (MRI). Because of its hyperdensity, tumors with high nucleus/cytoplasm ratio like lymphoma were kept in mind in the differential diagnosis. Similarly, due to the hypointensity of the mass, pseudo tumor orbita was considered. After the confirmation of retroorbital hematoma with the incisonal biopsy, the patient underwent emergency enucleation and implantation.

No premedication was applied in her anesthetic management. Pulse-oxymetry, non-invasive blood pressure, capnography, temperature measurements and ECG were monitored. Hypercarbia, hypocarbia and hypothermia were avoided. Anesthetic agents with no or minimal hepatotoxicity were used to avoid further hepatic deterioration. An inhalation agent, sevoflurane, which had minimal hepatotoxic potential, was used for the induction of anesthesia, and maintenance was provided by O_2/N_2O mixture and propofol infusion (10 mg/kg/hr) with additional fentanyl (0.1 μg/kg) A 5.5 mm ID uncuffed endotracheal tube was used in intubation. For muscle relaxation, cis-atracurium, which has elimination independent from hepatic clearance, was used at a dosage of 0.2 mg/kg intravenously. At the end of operation, the cis-atracurium was antagonized with 0.01 mg/kg atropine and 0.076 mg/kg neostigmine. No complication was seen during or after the operation. The patient was discharged from the hospital on the second postoperative day with her routine daily medication.

Discussion

Patients affected with Byler's disease present with jaundice, pruritus or hepatomegaly. Hepatomegaly is noted on physical examination at presentation, accompanied occasionally by splenomegaly. Laboratory tests demonstrate cholestasis, with elevated serum bile acids, alkaline phosphatase, and usually bilirubin, without hyperlipidemia.

Children with Byler's disease or another type of familial intrahepatic cholestatic syndrome may present to the anesthetist with a wide spectrum of clinical conditions ranging from mild cholestatic jaundice with normal liver function to the end stage liver failure, or as an emergency with bleeding esophageal varices. In addition to the normal pediatric clinical examination, the hepatic function tests and nutritional status of the child should be carefully examined. Fluid balance, temperature control and estimation of blood loss can cause problems before or during anesthesia. As cyanosis is not easily recognized in severely jaundiced children, hypoxemia is likely to present. The measurement of arterial hemoglobin oxygen saturation (SpO_2) with a pulse oxymeter is not useful in hyperbilirubinemia, and blood gas analysis is not necessary until SpO_2 is >90%[3]. As the SpO_2 was 99% with 50% O_2, we did not use invasive blood gas analysis. Use of invasive methods (arterial and central venous lines) in addition to pulse oxymetry, capnography, non-invasive blood pressure, ECG and temperature monitoring should be adapted to the child's clinical condition and the importance of the procedure.

When choosing the drugs to be administered to a child with Byler's disease, one should first consider the clinical stage of the disease. In addition to the usual preoperative pediatric examination, hepatic function and nutritional status should be carefully evaluated. In all cases anesthetic agents with no or minimal hepatotoxicity should be used to avoid further deterioration of liver unction. For this reason we used propofol infusion for maintenance of anesthesia, which has known considerable extrahepatic metabolism and no effect on liver blood flow[4]. In the presence of decompensated liver disease (hypoalbuminemia, prolonged prothrombin time, ascites and/or encephalopathy) the dose of these agents should be titrated according to the patient's response, bearing in mind that hypoalbuminemia reduces the protein binding of intravenous agents. Less propofol may be needed for induction, and the dose should be titrated according to the patient's response. In addition, as opiates may cause spasm of the sphincter of Oddi, their usage in patients with intrahepatic cholestasis or posthepatic obstruction should be cautiously considered. Patients with liver disease have variable requirements for non-depolarizing muscle relaxants. Muscle relaxants do not affect hepatic blood flow but their duration of action is longer. Plasma potassium may be raised and succinylcholine is relatively contraindicated. Cis-atracurium's elimination does not depend on the liver and can be used safely. For this reason we chose cis-atracurium which undergoes Hoffman elimination to form laudanosine and the monoquarternary acrylate metabolite[5]. Atracurium may be another choice because its metabolism, owing to spontaneous Hoffman's reaction and non-specific plasma esterases, is independent of the liver.

Tracheal intubation must be done gently due to probably existing esophageal varices. Cricoid pressure should be applied in presence of ascites. In our patient an experienced anesthetist gently performed the intubation with a 5.5 mm ID endotracheal tube without cuff. During controlled ventilation, care should be taken to avoid high airway pressures and hypocarbia because both reduce hepatic (arterial and portal) blood flow. Anesthetic agents with no or minimal hepatotoxicity should be used to avoid deterioration of liver function. Sevoflurane has been the inhalation agent of choice in cases of liver disease because it does not appear to have any hepatic toxicity and its effects on hepatic blood flow are similar to those of isoflurane[6]. In addition to sevoflurane, volatile agents such as halothane, enflurane, isoflurane and desflurane produce trifluoroacetyl acid (TFA), which, being a hapten, induces hypersensitivity[7]. This may increase liver injury after second exposure to TFA. It has been demonstrated that multiple administrations of sevoflurance in monkeys induce transient increases in serum concentrations of liver enzymes without gross pathological, histopathological or ultrastructural differences[8]. Owing to these untoward effects, we preferred sevoflurane for induction this case. After venous access establishment and induction with sevoflurane we started propofol infusion for maintenance of anesthesia. It is preferable to avoid halothane in these patients since it causes the most significant decreases in total hepatic blood flow.

The chosen technique for patients with any kind of familial intrahepatic cholestatic syndrome should take into account avoiding hypoxia, hypercarbia, hypocarbia and hypotension[9]. The anesthetist should have all the data about a patient so the choice of anesthetic agent could be tailored according to the type and duration of the planned procedure.

As anesthesia was conducted according to these anesthetic principles, our patient had a safe and effective anesthetic period and was discharged from the hospital within a few days without complication.

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