Chapter 30
Inborn Errors of Metabolism

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A 3-month-old presents for open liver biopsy with a suspected diagnosis of glycogen storage disease type I (von Gierke). He weighs 4.2 kg and was a term birth without any complications. VS: BP 86/54, HR 124, and RR 36.

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Preoperative Evaluation

Questions

1. What problems would you expect? Why didn't this show up earlier? Is this typical? Atypical?
2. What phy.sical characteristics will you see on exam that are of concern to you as an anesthesiologist?

3. What physiological derangements should you anticipate?

4. Any particular considerations for intravenous fluid management?

5. Does the hepatomegaly occur together with splenomegaly and are there any specific consequences you would have to worry about?

Preoperative Evaluation

Answers

1. and 2. In glycogen storage disease type I (von Gierke's disease), there is a deficiency of glucose-6-phosphatase, and glycogen accumulates in the liver, kidneys, and intestines. Excess glucose-6-phosphate enters the anaerobic glycolysis pathway leading to accumulation of lactic acid. The first sign that typically shows up is an increase in abdominal girth. Their first symptoms related to hypoglycemia may occur at about this age because they have been fed so frequently previously, but as they start sleeping more and going for longer periods of time without eating, symptomatic hypoglycemia may occur. This is typical. Findings may be very generalized, like heat intolerance, poor growth, or low muscle tone. More specific symptoms may relate to hypoglycemia, including seizures. Easy bruising may occur. Accompanying lactic acidosis may result in a compensatory respiratory alkalosis and hyperpnea. A large belly is often the initial focus. This is of concern with regard to gastric emptying and adequacy of respiration, all of which will get worse with the induction of general anesthesia. Muscle does not normally contain the enzyme glucose-6-phosphatase so neither cardiac nor skeletal muscle is involved in this disease. These children may also have impaired function of platelets and neutrophils and so may be subject to bacterial infection or have a prolonged bleeding time [1].

3. Hypoglycemia, lactic acidosis, and elevation of free fatty acids. Children should not be fasted for more than 3 h and blood glucose should be checked. The blood glucose level is often less than 40 if children have been fasted longer. Triglycerides and cholesterol are typically elevated. Special diets enriched with complex carbohydrates are common and must be included in the preoperative preparation of the patient. Cornstarch has been used for decades.

4. Alternatively, patients may be admitted the night before for intravenous glucose therapy and enteral carbohydrate therapy with close monitoring; nevertheless, the blood glucose is important to check prior to surgery. Some of these patients may have severe hypoglycemia and not show clinical signs and symptoms, perhaps because the brain can utilize the lactate as an energy source when glucose availability is limited. Intra-op, glucose-containing solutions should be given and glucose checked frequently.

5. The spleen is not enlarged. Nevertheless, the increase in abdominal girth is a consideration for mask induction, adequacy of respiration especially spontaneous respiration, and the influence the enlarged liver has on gastric emptying.

Intraoperative Course

Questions

1. Induction method?

2. Choice of monitoring?

3. How would you constitute intravenous fluids? Why?

Perioperative Management

Questions

1. How should glucose be managed postoperatively and how will you monitor the effectiveness of your strategy?

2. The patient is having difficulty with control of recurrent epistaxis after you placed an NG tube following induction. They are waiting for discharge as a day surgery patient. Should you delay discharge? Is this normal? Can you reassure the parents that the epistaxis will resolve? Should the nose be packed?

Intraoperative Course

Answers

1. Because of the protuberant abdomen, strong consideration should be given to a rapid sequence induction with endotracheal intubation even for a "simple" case like a liver biopsy. For any case lasting longer than an hour, a second IV large enough to withdraw blood samples or an arterial line should be placed for frequent glucose monitoring. Alternatively, point of care testing methods may be used when appropriate for minor cases or outpatient surgery. The key is the frequency of glucose monitoring and the plan for administration of complex carbohydrates as well as simple glucose for rescue [2].

2. Invasive monitoring is not needed for this case, but an extra line to draw blood from would be a convenience. For glucose monitoring, finger-stick point of care testing may be used as well, but I would reserve this for minimally invasive cases of short duration.

3. A 10 % dextrose infusion should be administered at 1.5–2X maintenance, with electrolytes as needed. D10 NS would be a good choice for most patients; nephropathy associated with GSD Type I will influence this choice as well. Lactated Ringer's should be avoided because of the lactate. The glucose infusion should be titrated to a blood glucose level greater than 70 mg%.

Perioperative Management

Answers

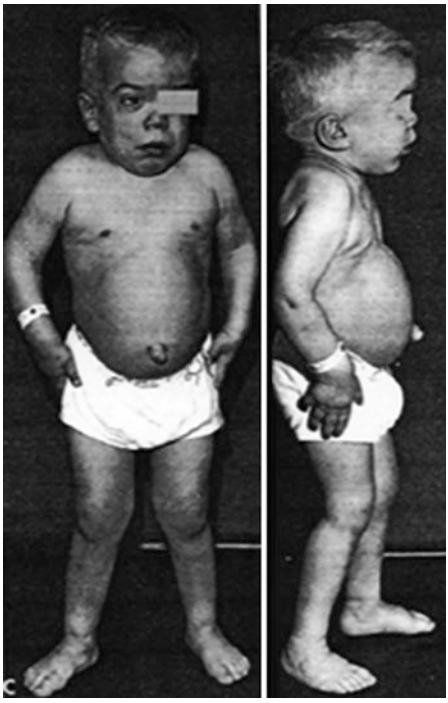
1. Glucose-containing IV fluid should be continued until the patient is taking POs and is checked for an acceptable glucose level. The progression of weaning from IV to PO glucose-containing fluid should be slow, and the glucose should probably be rechecked, making sure that the parents know that they should be checking the glucose at home as well.

2. Prolonged bleeding is not uncommon in these patients; the reasons are unclear. Normoglycemia will actually help the bleeding tendency, but nasal trauma should be ruled out by a nasal exam and the patient closely followed in the PACU until the bleeding stops.

Additional Questions

Questions

1. A 5-year-old with Hurler syndrome needs a recurrent umbilical hernia repaired. He cannot come in for evaluation prior to surgery, but will be coming in early on the day of surgery for his pre-op work-up. He is not yet in school and is 24 kg.



   (a) What is the basic defect? Are there any significant comorbidities?
   (b) How do they affect your anesthetic plan?
   (c) What is the significance of the protuberant abdomen and enlarged liver and spleen?
   (d) How does this disease affect the cardiovascular system?
   (e) Do you think this patient has restrictive or obstructive lung disease? Should PFT's or arterial blood gases be obtained preoperatively?

2. Why are infants tested for phenylketonuria? What are the consequences of a deficiency of phenylalanine hydroxylase? Can this be managed adequately by reduction of phenylalanine? Let's say that you had to do a gastrostomy in a patient with PKU who was 5 years old with an IQ of 20. Any special anesthetic considerations?

Additional Questions

Answers

1. Lysosomal Storage Disease: Hurler Syndrome
   (a) Mucopolysaccharidosis IH, called Hurler's disease, is one of a group of inherited disorders resulting from defects in degradation of complex mucopolysaccharides (now called glycosaminoglycans). Affected patients lack the lysosomal hydrolases responsible for degradation of these compounds. The lysosomes become engorged with mucopolysaccharides. The compounds dermatan and heparan, formed in excess as a result of defects in degradation of the glycosaminoglycans (formerly known as mucopolysaccharides), accumulate in virtually all tissues of the body.
   (b) Because you have to assume that glycosaminoglycans infiltrate all tissues, morbidity will be related to immobility. This especially includes the airway but also affects cardiac contractility and electrical conduction, the neck, and all joints including the cervical spine. The enlarged chest with limited rib excursion makes performing tracheostomy, especially in an emergency, very difficult. The liver and spleen are enlarged as a result of these accumulated glycosaminoglycans as well, similar to the tongue and other connective tissues [3].
   (c) The liver and spleen are enlarged as a result of accumulation of incompletely degraded mucopolysaccharides, similar to the tongue and other connective tissues. Physical as well as physiological impairments may result.
   (d) There is distortion of the valves and coronary artery deformation, again from accumulation of incompletely degraded glycosaminoglycans. In addition, the walls of the coronary arteries are thickened in these patients. Cardiac function is impaired in these children as a result of both coronary artery disease and deposition of glycosaminoglycans in the myocardium.
   (e) The ribs are flared and these patients have frequent respiratory infections. Accumulation of material within the chest wall may lead to a restrictive pattern of disease, while airway narrowing due to accumulation of the same by-products may give an obstructive pattern. This child will not cooperate with measurement of pulmonary function. If the serum bicarbonate is elevated, measurement of blood gases will help quantify the degree of preoperative respiratory insufficiency.

2. PKU is caused by the absence of the enzyme phenylalanine hydroxylase, which degrades the essential amino acid, phenylalanine, via the tyrosine pathway. In PKU, the excess phenylalanine not used in protein synthesis is transaminated to phenylpyruvic acid or decarboxylated to phenylethylamine. These and other metabolites as well as phenylalanine itself disrupt normal metabolism and cause CNS damage. Affected newborns are normal at birth but if untreated may lose as

3. An 8-year-old with a history of familial hypercholesterolemia type II B is scheduled for a portacaval shunt as a last-ditch treatment effort to lower his cholesterol; he is treated with cholestyramine and clofibrate. Dietary treatment has been of no benefit. His preoperative ECG shows Q waves in leads II, III, and avF and leads V4–V6. What are your thoughts about management? Do you think he is homozygous or heterozygous for this disorder? What difference does it make? What if his brother was heterozygous?

4. A community pediatric dentist calls to ask your advice about a 4-year-old who has been scheduled for office-based dental rehab with sedation. The patient has OTC syndrome (ornithine transcarbamylase deficiency, a disorder of the urea cycle). He typically uses a 50 % fixed mixture of nitrous oxide and oxygen (Entonox) and occasionally gives some PO midazolam for “difficult” children. What are your thoughts?

much as 50 IQ points in the first month of life. Severe vomiting occurs early on and the condition can be misdiagnosed as pyloric stenosis. Treatment is dietary, with rigid control of phenylalanine intake for at least the first 6 years of life and some lifelong control as well. An older child with PKU should not be seen in countries with screening, but a 5-year-old with untreated PKU has severe mental retardation, microcephaly, increased tone, growth failure, a prominent maxilla, and widely spaced teeth. The airway may be difficult. These children generally have fair skin with seborrhea and blue eyes. Clinically, an anesthetic should take into account the interactive pharmacology of current anticonvulsant medications, the use of pro-convulsant anesthetics, the effect of prolonged fasting on hypoglycemia, and therefore the creation of a catabolic state of elevated endogenous stores of phenylalanine precursors and the potential effect of prolonged use of nitrous oxide on methionine synthetase in case the patient is also vitamin B_{12} deficient.

3. Familial hypercholesterolemia is inherited as a dominant disorder. Patients who are heterozygous often do not develop coronary atherosclerosis until the third or fourth decade of life. By age 60, 85 % of these individuals have suffered an MI. The rare (1:1,000,000) patient who is homozygous for the abnormality in lipoprotein metabolism has a much more severe form of the illness. These patients have plasma cholesterol levels of >600 mg%. Dietary management is of little or no help in lowering the cholesterol. Cholesterol-lowering medications also offer little benefit. Coronary disease is evident by 10 years of age, and most patients die by 30 years of age. Therapies such as plasmapheresis, ileal bypass surgery, and portacaval shunt placement have had some success. Liver transplantation has helped several patients. There is a possible genetic treatment involving transfecting the patient's own hepatocytes with a gene for the missing receptor.

4. Many of the urea cycle disorders have similar clinical presentations due to the hyperammonemia, respiratory alkalosis, and neurological symptoms (encephalopathy, seizures, signs and symptoms of cerebral edema such as vomiting and headaches) [4, 5]. Sedation or anesthesia may precipitate an acute metabolic encephalopathy. Extreme care to evaluate pre- and post-procedure acid base status and ammonia levels should be taken. Fasting must be minimized in order to avoid hypoglycemia and catabolism, and facilities for administering intravenous glucose must be readily available. Particularly with regard to oral procedures, gastrointestinal absorption of blood may worsen the encephalopathic picture or precipitate seizures. Seizures are common and should be anticipated. For clinically significant hyperammonemia, intravenous nitrogen scavengers such as sodium benzoate or sodium phenylacetate should be available. Steroids (typically used for antiemetic prophylaxis) should be avoided because they increase catabolism.

5. An 8-year-old is scheduled for muscle biopsy, brainstem auditory evoked potentials, echocardiogram, and eye exam under anesthesia. He has mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) syndrome. What would you like to know about him BEFORE he comes to the operating room for his anesthetic and diagnostic tests? What problems do you anticipate? How will you "design" your anesthetic technique?

5. At 8 years of age, it is likely that much is known about this patient qualitatively but not quantitatively. It should be anticipated that he might have some cardiac functional abnormalities like cardiac myopathy as well as cardiac conduction abnormalities like varying degrees of heart block. It would not be surprising if he had some degree of respiratory insufficiency on a chronic basis. Similar to many other metabolic disorders, prolonged fasting will tend to make MELAS syndrome worse, so the NPO time should be minimized or supplemental glucose provided. Lactated Ringer's may not be the best IV fluid to use because of the baseline lactic acid elevation. The use of succinylcholine is controversial because of the risk of hyperkalemia, but exaggerated responses to nondepolarizing muscle relaxants have been reported. Acid-base status must be followed closely. Five percent of patients have diabetes. Various anesthetic techniques have been reported, the most common being total intravenous anesthesia although the full range of anesthetic medications have been utilized. Perioperative hyponatremia and hyperkalemia have been noted [6, 7].

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