5. Mathieu A, Dalton B, Fischer JE, et al: Expanding aneurysm of the radial artery after frequent puncture. ANESTHESIOLOGY 38:401–403, 1973
6. Dalton B, Laver MB: Vasospasm with an indwelling radial artery cannula. ANESTHESIOLOGY 34:194–197, 1971
7. Katz AM, Birnbaum M, Moylan J, et al: Gangrene of the hand and forearm: A complication of radial artery cannulation. Crit Care Med 2:270–272, 1974
8. Downs JB, Rackstein AD, Klein EF, et al: Hazards of radial artery catheterization. ANESTHESIOLOGY 34:194–197, 1971
9. Lowenstein E, Little JW III, Hing HL: Prevention of cerebral embolization from flushing radial artery cannulas. N Engl J Med 285:1414–1416, 1971
10. Gaan D, Mallick HP, Brewis RAL, et al: Cerebral damage from declotting Scribner shunts. Lancet 2:77–79, 1969
11. Conrad MC: Functional Anatomy of the Circulation to the Lower Extremities. Chicago, Year Book Medical Publishers, 1971
12. Gray H: Anatomy of the Human Body. Twenty-ninth edition. Philadelphia, Lea and Febiger, 1973
13. Barnhorst BA, Boener HB: Prevalance of congenitally absent pedal pulses. N Engl J Med 278:264–265, 1968
14. Huber JF: The arterial network supplying the dorsum of the foot. Anat Rec 80:373, 1941
15. Carter SA: Response of ankle systolic pressure to leg exercise in mild or questionable arterial disease. N Engl J Med 287:578–582, 1972
16. May AG, Van de Berg L, DeWeese JA, et al: Critical arterial stenosis. Surgery 54:250–259, 1963
17. Furman EF, Hairabet JK, Roman DG: The use of indwelling radial artery needles in paediatric anesthesia. Br J Anaesth 44:531–532, 1972
18. Jones MV, Craig DB: Venous reaction to plastic intravenous cannulae, influence of cannula composition. Can Anaesth Soc 19:491, 1972

Hazards of Anesthesia and Operation in Maple-syrup-urine Disease

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Maple-syrup-urine disease, or branched-chain ketonuria, is a metabolic disorder involving the branched-chain amino acids leucine, isoleucine, and valine (fig. 1).[1] The metabolic defect appears to involve oxidative decarboxylation of the metabolites, alpha keto acids (fig. 2). The result is an accumulation of these keto acids and the amino acids themselves in blood and urine. The latter has the odor of maple syrup. This same sweet caramel-like odor is also apparent in other secretions such as perspiration and cerumen. Although the exact source of this is unknown, the alpha keto acids also have a similar odor in small amounts. Despite the fact that all of the metabolites proximal to the block accumulate, the deleterious effects seem most clearly related to elevated levels of the amino acids themselves. The characteristic clinical picture appears within the first five days of life: poor feeding habits, progressing to lethargy and convulsions. The diagnosis is suggested by the characteristic odor of the urine and confirmed by high blood levels of branched-chain and alpha keto acids, and demonstration of the metabolic block in peripheral leukocytes or fibroblasts in the skin.[2] Although dietary therapy is associated with prolongation of survival, mental retardation and permanent neurologic signs usually result. This is largely because most foods have a high content of branched-chain amino acids, and a normalized diet with stringent withdrawal of the compounds is not easily achieved.

Since the initial description of maple-syrup-urine in 1954, nearly 100 cases have been reported. The frequency of this disease with severe symptoms is estimated to be about one in 250,000 live births.[3] Recently, however,

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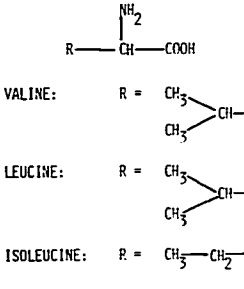

FIG. 1. Structural formulas for the branched-chain amino acids: leucine, isoleucine, and valine.

additional variant forms in which symptoms are delayed in onset, sometimes intermittent, and the neurologic disease milder have been described.[4] The following report describes such a case and illustrates the need to be aware of the metabolic consequences of operation and anesthesia in patients who have this uncommon but precarious disorder.

REPORT OF A CASE

A 6-year-old girl was scheduled for bilateral myringotomies and removal of tonsils and adenoids. Although the prenatal and neonatal courses had been unremarkable, she had been evaluated at the age of 16 months because of slow motor development. The chief complaint at that time had been inability to sit without support. Examination disclosed a high acetone content in the urine, which also had peculiar odor resembling burnt sugar or maple syrup. Paper chromatography of blood and urine samples demonstrated marked elevations of leucine, isoleucine, and valine, as well as ketoacidemia and ketonuria, confirming the diagnosis of maple-syrup-urine disease. The patient's normal diet (6 grams of protein per day) was altered to a diet with a low protein content, consisting of applesauce, bananas, pears, peaches, green beans, beets, carrots, rice cereal, Kool-ade, and cola. She continued to thrive on this diet, but her mental development was slow. Hospitalization was necessary at the age of 4 years, when vomiting and dehydration associated with tonsillitis and otitis resulted in lethargy, convulsions, and ketoacidosis. Subsequent episodes of otitis prompted admission for the present operation.

Physical examination on admission disclosed that the patient was of average height and weight for her age but had moderate mental retardation. Other abnormal findings were limited to the tonsillar hypertrophy. The urine was free of sugar and acetone, and blood urea nitrogen and creatinine were 10 and 0.5 mg/100 ml, respectively. Fasting blood glucose was 88 mg/100 ml on the morning of operation (the patient had been encouraged to take clear liquids *ad lib.* until six hours prior to the scheduled operation).

The patient arrived unpremedicated in the operating room, where an intravenous infusion of 5 per cent dextrose in Ringer's lactate solution was begun. Anesthesia was induced with thiopental, 50 mg, iv, and maintained with 1–1.5 per cent halothane and 60 per cent nitrous oxide in oxygen (total flow 5 l/min) with controlled ventilation. Endotracheal intubation was accomplished easily without the aid of a muscle relaxant. The operation was completed in 60 minutes and the anesthetic course was uneventful except for a transient episode of what appeared to be ventricular bigeminy midway into the procedure. A sample of forearm venous blood at this time had a *p*H of 7.32 and P_{CO_2} of 42 torr. A Dextrostix (Ames) indicated a blood glucose level of about 175 mg/100 ml.

The patient awoke promptly in the recovery room, where the intravenous solution was changed to dextrose 10 per cent, in water, with 25 mEq/l Na^+ and 25 mEq/l K^+. Blood glucose an hour later was 140 mg/100 ml and the venous blood *p*H was 7.35. Both blood and urine were negative for acetone. There was no problem with postoperative bleeding, and the patient resumed her regular diet that evening. She was discharged well on the second postoperative day.

DISCUSSION

The approach to anesthesia in a case such as this does not involve the selection of a particular technique, but rather, recognition of the metabolic hazards of the stress of anesthesia and operation. Our patient was exposed to these potential stresses because of repeated infections. Any infection in such patients is very serious, often necessitating hospitalization.[3] Anorexia and vomiting progress quickly to lethargy, ataxia, and convulsions. These attacks presumably result from the catabolism of body proteins, which have a high content of branched-chain amino acids. The stress associated with operation is likewise hazardous, since tissue catabolism and protein breakdown invariably occur. An added metabolic load may result from absorption of blood in the gastrointestinal tract, which might

occur in procedures such as tonsillectomy. This is particularly true if bleeding occurs postoperatively and is not adequately recognized. The only previous report involving surgery in the case of a patient with a mild form of the disease emphasizes the potentially lethal nature of this problem.[4]

Although the elevation of branched-chain amino acids is presumably the cause of neurologic deterioration, the high levels of the alpha keto acids have significant metabolic consequences themselves. Since they represent a large pool of non-metabolizable acids, systemic acidosis usually results. Therefore, it is important to monitor blood *p*H in these patients and correct with bicarbonate if necessary. During anesthesia, forearm venous blood may provide an adequate source of blood obviating the need for arterial puncture.[6]

Another significant metabolic hazard in these patients is their tendency to develop hypoglycemia.[7] The hypoglycemic episodes probably result from excessively high leucine levels, which can lower blood glucose in normal subjects. Although the mechanism remains obscure, it is probably related to the effect of leucine on intestinal transport of glucose or to hyperinsulinism, since leucine has been shown to stimulate insulin release.[8] In the surgical patient the danger of hypoglycemia is further enhanced by the customary overnight fast. For this reason it is advisable to measure blood glucose and begin glucose infusion well in advance of anesthesia and operation.

Several investigators have reported increased glucose levels and a decreased response to insulin associated with halothane anesthesia and surgical stimulation.[9,10,11] However, there is no way to predict the responses of patients with maple-syrup-urine disease because of the levels of leucine that may be present. Thus, it is important to infuse a glucose solution and measure blood glucose during anesthesia. During the recovery period, when hypoglycemia may continue to be a threat, the slow administration of a more concentrated glucose solution (10 per cent) with appropriate electrolytes is desirable. Glucose is also important as a source of calories, since these patients are apt to break down their own body protein in the absence of adequate nutrition. As a result, the branched-chain amino acids and keto acids accumulate.

Awareness of these problems also assumes great importance in mild variants of the disease, such as our patient had. Individuals thus afflicted do not appear severely ill, yet they may die in acute metabolic decompensation.[4] By providing sufficient caloric support, monitoring blood glucose and *p*H, and promptly instituting corrective measures, the anesthesiologist can minimize the metabolic derangements that appear during the stressful period of anesthesia and operation.

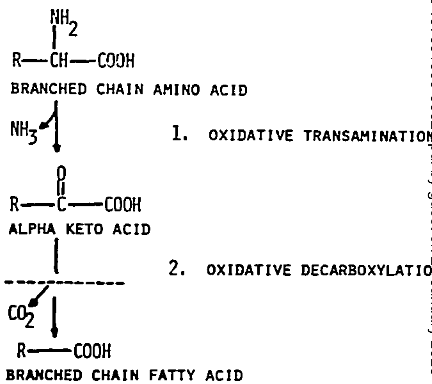

FIG. 2. Metabolic degradation of the branched-chain amino acids, showing the location of the proposed metabolic defect, *i.e.*, the oxidative decarboxylation of alpha keto acids.

REFERENCES

1. Dancis J, Levitz M: Abnormalities of branched-chain amino acid metabolism, The Metabolic Basis of Inherited Disease. Edited by JB Stanbury, JB Wyngaarden, DS Fredrickson. New York, McGraw-Hill, 1972, pp 426–439
2. Dancis J, Hutzler J, Snyderman SE, et al: Enzyme activity in classical and variant forms of maple syrup urine disease. J Pediatr 81:312–320, 1972
3. Scriver CR, Rosenberg LE: Amino acid metabolism and its disorders, Major Problems in Clinical Pediatrics. Volume X. Edited by AL Schaffer. Philadelphia, W. B. Saunders, 1973, pp 263–273
4. Dancis J, Hutzler J, Rokkones T: Intermittent branched-chain ketonuria, a variant of maple syrup urine disease N Engl J Med 276: 84–89, 1967
5. Harris RJ: Infection in maple syrup urine disease. Lancet 2:813–814, 1971
6. France CJ, Eger EI II, Bendixen HH: The use of peripheral venous blood for *p*H and carbon dioxide tension determinations during general anesthesia. ANESTHESIOLOGY 40:311–314, 1974
7. Donnell GN, Lieberman E, Shaw KNF, et al: Hypoglycemia in maple syrup urine disease. Am J Dis Child 113:60–63, 1967
8. Mabry CC, DiGeorge AM, Auerbach VH: Leucine induced hypoglycemia. II. The blood glucose depressant action of leucine in normal individuals. J Pediatr 63:295–302, 1963
9. Merin RG, Samuelson PN, Schalch DS: Major inhalation anesthetics and carbohydrate metabolism. Anesth Analg (Cleve) 50:625–632, 1971
10. Allison SP, Tomlin PJ, Chamberlain MJ: Some effects of anesthesia and surgery on carbohydrate and fat metabolism. Br J Anaesth 41:588–592, 1969
11. Clarke RSJ: The hyperglycaemic response to different types of surgery and anesthesia. Br J Anaesth 42:45–52, 1970

Perinatology

FETAL TRANSFUSION Maternal and fetal hemodynamics, placental blood flow, fetal–placental blood volume, and fetal blood volumes were measured in six chronic sheep preparations to evaluate changes during acute fetal hypoxia induced by maternal hypoxia. During fetal hypoxia, the maternal and fetal arterial blood pressures and heart rates were essentially unchanged. Placental blood flow (control = 325 ml/kg/min) was also unchanged during the hyposic period. However, the placental blood volume decreased significantly from 65 to 60 and 51 ml/kg after 15 and 30 minutes of hypoxia, respectively. Fetal blood volume increased reciprocally and significantly from 86 to 109 and 102 ml/kg after the same periods of hypoxia, since the fetal–placental blood volumes were unchanged. These blood volume changes persisted for 30 to 60 minutes following cessation of hypoxia. Placental vascular resistance, measured in six experiments, showed a significant increment during hypoxia, suggesting placental vasoconstriction as the responsible mechanism for the reduction of placental blood volume and reciprocal increase in fetal blood volume. The data suggest that significant placental transfusion to the lamb fetus may occur *in utero* during fetal hypoxia, resulting in a higher fetal blood volume before birth. *(William OH, and others: Placenta to Lamb Fetus Transfusion in Utero during Acute Hypoxia. Am J Obstet Gynecol 122: 316–322, 1975.)*

NEONATAL SCALP INFECTION This communication relates a case report of fatal scalp infection in a newborn infant. Fetal heart rate monitoring *in utero* was performed with the widely used spiral scalp electrode. At birth, the puncture mark was evident, and the infant did well until 14 hours of age, when an apneic episode occurred, followed by lethargy. X-ray of the head revealed air density in the tissues of the right occipital area. The infant did poorly and died at 44.5 hours of age. Cultures taken from the pneumatized scalp and the infant's blood grew *E. coli*. This apparently is the first time fetal scalp electrodes have been implicated as the cause of a fatal complication. *(Turbeville DF, and others: Complications of Fetal Scalp Electrodes: A Case Report. Am J Obstet Gynecol 122: 530–531, 1975.)*

ABSTRACTER'S COMMENT: The rewards of fetal monitoring far outweigh the dangers. Could this complication be prevented by prepping the presenting part (portion of scalp accessible through the cervix) with povidone–iodine?