I. Introduction

Inborn metabolic disorders are individually rare and collectively common. The primary-care physician is likely to encounter these conditions: (1) in the newborn nursery in the context of neonatal diagnostic screening programs and in the differential diagnosis of infants with apparent septicemia, lethargy, coma, and seizures; (2) in the emergency room in the differential diagnosis of hypoglycemic or hyperammonemic coma; (3) in the office, clinic, or hospital, in the differential diagnosis of seizure disorders, muscle weakness, developmental delays, failure to thrive or liver failure; and (4) in the investigation of cases of neonatal death and sudden unexplained infant death.

II. Objectives

This material should be of help to the student in:

1. Selecting screening procedures for possible metabolic disease in a neonate with:
   a. severe jaundice and a septicemia-like picture awaiting culture proof,
   b. lethargy and hyperventilation,
   c. lethargy, vomiting, an increased anion gap, and neutropenia.

2. Recommending appropriate diagnostic steps for a previously healthy six-month-old infant who develops a febrile illness with vomiting, then presents with a hypoglycemic seizure and hepatomegaly; the initial urine specimen is found to be free of acetone.

3. Ordering appropriate diagnostic procedures for a female patient with a long-standing history of protein aversion who develops a febrile illness with vomiting, and then becomes confused, combative, and progressively obtunded.

4. Recommending appropriate diagnostic steps for an infant or child with marked hepatomegaly and hypoglycemia.

5. Explaining, as one would to a parent, the general treatment plan for phenylketonuria, galactosemia, homocystinuria, an organic acidemia, a $-oxidation defect, a urea cycle defect, or hepatic glycogen storage disease.

III. Background Concepts

Metabolic diseases fall into several distinctive categories, including the classical pathway defects, diseases of transport function, lysosomal storage diseases, peroxisomal diseases, and respiratory chain defects.

CLASSICAL PATHWAY DEFECTS are the prototype historical inborn errors of metabolism. In each of these diseases, a unique, unduplicated mainstream catabolic pathway is rendered nonfunctional by a missing or defective enzyme. Enzyme substrate accumulates and often finds its way, sluggishly, into accessory pathways. Enzyme product is low or absent. These diseases are often amenable to diet therapy. Key examples are the following:

1. Phenylketonuria. In this disease, the sole pathway for metabolism of phenylalanine to CO2, H2O, and urea is blocked at the first step in the pathway:

   ![Phenylalanine metabolic pathway diagram]

   Marked elevation of phenylalanine levels in body fluids causes interference with postnatal brain development and leads to profound mental retardation. Dietary treatment which restricts the intake of phenylalanine and supplements tyrosine can prevent the mental retardation.
2. **Galactosemia.** In this disease, the sole pathway for conversion of the monosaccharide galactose to glucose is blocked at a key step:

\[
\text{Galactose} \rightarrow \text{Galactose-1-P} \rightarrow \text{UDP-Galactose} \rightarrow \text{UDP-Glucose} \rightarrow \text{Glycogen}
\]

Intracellular galactose-1-phosphate is toxic to neurons, hepatocytes, and leukocytes, resulting in brain injury, cirrhosis, and impaired defenses against bacterial infection. Galactose is reduced to a six-carbon alcohol (galactitol), in an accessory pathway. Galactitol is responsible for opacifying the lenses and producing cataracts. Females with classical galactosemia uniformly have primary ovarian failure due to some unknown toxic effect of galactose or galactose phosphate. On first exposure to milk feedings, the galactosemic infant typically becomes ill within a few days, with jaundice, lethargy, vomiting, and, very often, septicemia due to *E. coli*. This early phase of the illness is often fatal unless the disease is diagnosed and treated by means of strict galactose exclusion from the diet. Such treatment can minimize brain damage and prevent cirrhosis and cataract formation. Ovarian failure is not yet preventable because we do not yet understand the basic mechanism for its occurrence.

3. **Homocystinuria.** In this disease, the pathway for conversion of the sulphur-containing amino acid methionine to cysteine is blocked at a key intermediate step:

\[\text{Methionine} \rightarrow \text{Homocysteine} \rightarrow \text{Cystathionine} \rightarrow \text{Cysteine}\]

The excessive homocysteine disrupts the structure of some connective tissues, causing joint stiffness and dislocation of ocular lenses; mental retardation occurs due to unknown mechanisms; blood is hypercoaguable, possibly due to direct effects of homocysteine on platelet function, making homocystinuric patients subject to frequent thromboembolic phenomena. Generalized osteoporosis is a commonly associated finding. Treatment with a diet low in methionine and supplemented with cystine prevents mental retardation. Daily aspirin administration controls the hypercoagulability and minimizes the vascular complications.

4. **The hepatic glycogen storage diseases.** These result from defects in various enzymes responsible for glycogen breakdown: phosphorylase kinase, phosphorylase, debrancher enzyme, and glucose-6-phosphatase. Since glucose-6-phosphatase provides the final common chemical step for both glycogen breakdown and gluconeogenesis, deficiency of this enzyme (type 1 glycogen storage disease or von Gierke's disease) produces more severe hypoglycemia than any of the others, and because glucose-6-phosphate is a natural substrate for the glycolytic pathway, any stimulus to break down glycogen will produce lactic acidosis. By means of multiple small daytime feedings and continuous nighttime nasogastric feedings, these patients can be kept in a constant state of postprandial absorption with blood sugars maintained in the range 90-110 mg/dl, which is too low to stimulate glycogen formation and too high to stimulate glycogen breakdown. This minimizes many of the disease manifestations, decreases lactic acidemia and hyperuricemia, and improves growth.

5. **The organic acidemias.** A number of diseases can produce metabolic acidosis and acute neurotoxicity due to accumulation of organic acids. The four examples of such diseases to be described here typically produce symptoms during the first month of life, and in each case the excess organic acid is a product of protein catabolism most often provoked by fasting. This could be the fasting that any newborn infant experiences while making the transition from placental nutrition to breast or bottle feedings, or it could be the fasting which occurs during an acute illness. Branched-chain ketoaciduria (maple syrup urine disease) results from defective metabolism of all three branched-chain amino acids (leucine, isoleucine, and valine). It presents with lethargy, vomiting, and seizures. 10% glucose infusions to blunt fasting, hemodialysis to remove the toxic metabolites, and hyperalimentation with an amino acid mixture low in the branched-chain amino acids constitute recommended therapy during the acute stage. Isovaleric acidemia (odor-of-sweaty-feet syndrome) is due to defective leucine metabolism. It presents with lethargy, vomiting, dehydration, coma, and hypothermia. Acute episodes are treated with 10% glucose and bicarbonate infusions, glycine (which converts the toxic isovaleric acid to non-toxic isovalerylglucose) is given by mouth or nasogastric tube. Propionic and methylmalonic acidemia represent blocks in the catabolic pathway for several amino acids, all of which yield a three-carbon fragment (isoleucine, valine, threonine, methionine). The three-carbon fragment becomes propionyl Co A, which is converted to methylmalonyl Co A by carbon dioxide fixation. The methylmalonyl Co A is in turn isomerized to succinyl Co A, which can enter the Krebs cycle as succinic acid. Defective enzymes at strategic points in this sequence result in the diseases known as propionic acidemia and methylmalonic acidemia. Symptoms and signs include lethargy, vomiting, coma, acidosis, hyperventilation, and neutropenia. Characteristically, these symptoms appear during the neonatal period or at times of aggravated fasting during intermittent illnesses. Treatment consists of intravenous glucose and bicarbonate and a reduced protein intake.

6. **Congenital hyperammonemia** can result from any of several defective steps in the Krebs urea cycle, with resulting inefficient detoxification of the ammonia derived from the catabolism of amino acids. Severe defects in this cycle are incompatible with postnatal existence and produce lethal neonatal hyperammonemia. Partial defects (with residual low-level enzyme activity) are associated with
variable expression and variable severity of symptoms. The clinically most important example is ornithine transcarbamylase (OTC) deficiency. This x-linked condition is lethal in the hemizygous male because of severe neonatal hyperammonemia. It is variably expressed in the heterozygous female because early random inactivation (Lyonization) of the x chromosome may cause the defective gene to be represented in many cells or few. The affected female typically experiences difficulty at times of fasting during intercurrent illnesses, especially those with vomiting and fever. The first hyperammonemic crisis may occur at any time from infancy to adulthood, often with a fatal outcome or severe neurologic sequelae. Infants with OTC deficiency typically acquire an aversion to protein foods. Acutely, this condition is treated with a glucose infusion, to blunt the catabolism of protein, and with hemodialysis to remove ammonia. Sodium phenylbutyrate, given orally, combines with glycine and other nitrogen-containing metabolites to form excretible compounds, which to a small extent can substitute for urea formation.

In recent years, a number of hereditary defects have been recognized in the pathway for \( \beta \)-oxidation of fatty acids during the normal fasting state. Most of the body's energy is derived from this process of oxidatively splitting off two carbons at a time from long-chain (16C or 18C) fatty acids, using the acetyl CoA units directly for energy production in muscle. In liver, the process of \( \beta \)-oxidation yields ketone bodies (acetoacetate and 3-hydroxybutyric acid), which are exportable to other tissues, especially muscle, and utilized for energy under conditions of fasting. Thus \( \beta \)-oxidation is an important process, permitting the small amounts of glucose produced from gluconeogenesis to be used almost exclusively by the brain. \( \beta \)-oxidation takes place in the mitochondrion and carnitine is required for moving fatty acids across the mitochondrial membrane into the interior.

Medium-chain acyl CoA dehydrogenase deficiency is the most common of the currently recognized \( \beta \)-oxidation defects, with a frequency of about one in 15,000 births. \( \beta \)-oxidation of fatty acids of C8, C10, and C12 chain length is blocked because of the absence of a mitochondrial dehydrogenase specific for medium-chain-length fatty acids. Infants and children with this defect get along well while in good health, but at times of aggravated fasting (febrile illnesses, vomiting, or prolonged overnight fasting) may develop a Reye syndrome-like picture of acute hypoglycemia without ketonuria, along with fatty liver, dicarboxylic aciduria (C6,C8,C10) and carnitine depletion.

Acutely, this condition is treated with intravenous glucose, in order to maintain normoglycemia and inhibit lipolysis in adipose tissue, and with intravenous carnitine. During health, recommendations include a routine bedtime snack, to avoid a prolonged night-time fast, and oral carnitine supplementation. When caloric intake is interrupted by a febrile illness with vomiting, the child should be taken to an emergency room for intravenous glucose.

The diseases of transport function differ from the specialized pathway disorders just discussed in that the defective or absent gene product is not an enzyme protein but rather a protein which catalyzes transport of a metabolite across a biological membrane. Inheritance is typically autosomal recessive. Examples include: (1) cystinuria, in which there is a renal tubular defect in reabsorption of cystine, with the result that the urine contains this poorly soluble amino acid in excess and cystine-containing stones tend to form, (2) Hartnup disease, in which there is an intestinal defect in the absorption of tryptophan, with resulting symptoms of tryptophan deficiency and niacin deficiency, and (3) cystic fibrosis, in which there is defective transport of chloride ion across glandular epithelium.

The lysosomal storage diseases are characterized by progressive intra-lysosomal accumulation of a macromolecular protoplastmic constituent, which occurs because the lysosomes genetically lack a specific hydrolase which would normally convert an insoluble macromolecule (such as mucopolysaccharide, glycolipid or glycogen) into small and soluble molecules (such as monosaccharide, fatty acid, or glucose). These diseases are recessively inherited and typically are lethal in infancy or early childhood. Typically, the affected infant appears normal at birth. Effective treatment modes are not yet available, but this group of diseases may prove to be candidates for enzyme replacement in the future. Prenatal diagnosis is possible with most of these diseases by enzyme assay on cultured amnion cells. Glycogen storage disease type 2 (also known as Pompe's disease or glycogen storage disease of the heart) was the first lysosomal storage disease to be well delineated historically. Other examples include the Hunter-Hunter group of mucopolysaccharide storage diseases and the lipid storage diseases (Nieman-Pick, Gaucher and Tay-Sachs). The reticuloendothelial system tends to be prominently involved in the lipid storage diseases because erythrocyte membranes are lipid-rich. When these membranes are degraded in the reticulo-endothelial system in the absence of a particular lipase, the corresponding lipid accumulates as a storage material.

The peroxisomal diseases are a group of recessively inherited disorders resulting from abnormalities in the peroxisomes, which are subcellular organelles constituting the unique site of \( \beta \)-oxidation of very long-chain fatty acids and biosynthesis of bile acids and plasmalogens. The peroxisomal abnormality can be total absence of peroxisomes (as in the Zellweger syndrome) or selective deficiency of one or more enzymes normally found in the peroxisomes. In contrast to other inborn errors of metabolism, obvious or subtle dysmorphic features are commonly associated with this group of diseases. X-linked adrenoleukodystrophy presents as a progressive disturbance of gait and coordination, dysarthria, central and peripheral demyelination, and adrenocortical atrophy.

The respiratory chain defects represent a growing number of neuromuscular diseases now known to result from mitochondrial inheritance. In contrast to the more familiar nuclear inheritance with equal contributions from ovum and sperm, mitochondrial DNA derives exclusively from the mother. It codes for subunits of four of the five respiratory chain complexes (complex I, III, IV, and V). Thus, mutations can lead to defective oxidative phosphorylation, with disease manifestations most prominent in tissues having the highest energy demand (muscle and those parts of the central nervous system dealing with the special senses of sight and hearing). Muscle weakness and lactic acidemia are common manifestations. One example of these diseases is known as MERRF (mitochondrial encephalopathy with ragged red fibers). The ragged red fibers which give this
disease entity its name are accumulations of abnormal mitochondria seen on muscle biopsy.

IV. Lecture Outline (slide list)

1. Phenylketonuria, untreated
2. Maternal PKU syndrome
3. Galactosemia cataract
4. Homocystinuria
5. Dislocated lens
6. Marfan syndrome
7. Hepatic glycogen storage
8. Pompe disease, heart
9. Hurler syndrome
10. Hunter syndrome
11. Cherry-red spot of Tay-Sachs disease
12. Kayser-Fleischer ring of Wilson’s disease
13. Bone age chart
14. Wrist x-ray, bone age
15. Cystinosis, cornea
16. Cystinosis, bone marrow
17. Mitochondrial myopathy with ragged red fibers
18. Fasting intolerance, emergencies
19. Normal fasting state
20. Fasting in insulin-treated diabetes
21. Ketotic hypoglycemia
22. Alcohol ingestion
23. Defect in fatty acid oxidation
24. Urea cycle defect
25. Diagnosis and treatment: insulin-induced hypoglycemia
26. Diagnosis and treatment: ketotic hypoglycemia
27. Diagnosis and treatment: alcohol-induced hypoglycemia
28. Diagnosis and treatment: infant with MCAD
29. Diagnosis and treatment: little girl with OTC deficiency and hyperammonemia
30. Summary points, fasting emergencies

V. Additional Materials Available On Request (reach me at 559-7350 or hwiltse@unmc.edu)

A. A typed handout dealing with differential diagnosis of metabolic disease, including:
   1. The neonate in need of metabolic screening
   2. The neonate with a positive screening test result for phenylketonuria
METABOLIC PROBLEMS IN PEDIATRICS

3. The neonate with a positive screening test for galactosemia
4. The septic-appearing neonate with lethargy, vomiting, and jaundice
5. The septic-appearing neonate with lethargy, vomiting, and hyperventilation
6. The septic-appearing neonate with neutropenia
7. The neonate with seizures
8. The neonate with dysmorphic features, hypotonia and seizures
9. The infant or child with hypoglycemia, ketosis, and hepatomegaly
10. The infant or child with hypoketotic hypoglycemia
11. The child with dislocated ocular lenses
12. The child with undifferentiated mental retardation
13. The infant with hypotonia and muscle weakness
14. The infant who was normal at birth and subsequently is noted to have hepatomegaly and such features as stiffening of joints, coarsened skin and unusual facies
15. The infant with hyperacusis and developmental regression
16. The child with “progressive cerebral palsy”

B. Typical Laboratory Menu (UNMC lab but quite similar to other hospitals)
C. Metabolic glossary

VI. Supplemental Reading Material


LIFE-ThREATENING HYPOGLYCEMIA AND HYPERAMMONEMIA IN CHILDREN (TRANSCRIPT, SEPTEMBER 1998)

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A. Introduction

Some infants and children are poorly equipped to withstand a fast of more than a few hours duration. A longer-than-usual overnight fast or a vomiting illness may bring them to the emergency department with symptomatic hypoglycemia, hyperammonemia, or ketoacidosis. The patient arrives in an obtund state or convulsing, very typically during the morning hours. This discussion will address six types of conditions presenting in this manner. Prompt recognition and treatment by the emergency physician can often prevent a fatal outcome or permanent neurologic impairment.

B. The Major Clinical Scenarios Relating to Fasting Intolerance are as Follows:

1. Insulin-Treated Diabetes Mellitus. Any significant interruption in the prescribed caloric intake can leave the diabetic child susceptible to
varying degrees of hypoglycemia and a risk of neurologic injury. Most paramedic teams and emergency department personnel know this condition well and are expert at treating it.

2. **Ketotic Hypoglycemia.** This is the most common of the hypoglycemic disorders occurring in the preschool age group. It can present quite dramatically, but may be the most benign of this group of conditions.

3. **Ethanol Ingestion.** This is a hazard almost unique to the toddler age group. A hungry toddler who wanders the house unsupervised, before the parents are up, may find a left-over alcoholic beverage and sample it. The resulting hypoglycemia can be severe.

4. **Fatty Acid Oxidation Defects.** These are a recently recognized group of inborn metabolic disorders. They were essentially unheard of before the 1980's and are now known to be collectively as common as phenylketonuria (1:12,000 births). Unrecognized fatty acid oxidation defects probably contributed significantly to the epidemics of Reye syndrome which plagued emergency departments during the 1970's, and we currently speak of the "metabolic Reye syndrome" to denote the fatty liver and hypoglycemia which occur acutely in susceptible infants and children with these defects. The most common of the inherited fatty acid oxidation defects is MCAD (medium-chain acyl CoA dehydrogenase deficiency). During the fasting state, the infant or child with MCAD cannot effectively derive energy by burning fat or producing ketone bodies. Blood sugar falls drastically and alternative energy substrates are scarce. The MCAD metabolic crisis may occur when a previously healthy infant is making the transition from feedings every four hours to sleeping 8 hours through the night. Or it may occur with the first "aggravated fast", brought on by the combination of a febrile illness and vomiting. Hypoketotic hypoglycemia, the paradoxical absence of urinary ketones, is pathognomonic. MCAD is a serious threat only during infancy and early childhood. If we can get children with this defect safely through any metabolic crisis that occurs during their early years, their tolerance for fasting will improve greatly as they get older.

5. **Hyperammonemia Due to a Defect in the Urea Cycle.** Production of glucose from body protein by gluconeogenesis is an essential survival mechanism during fasting, since it helps to keep the brain supplied with glucose. Unfortunately, gluconeogenesis from protein involves release of ammonia, and for children with congenital defects in urea production, the ammonia cannot be efficiently detoxified. These infants and children will present, not with hypoglycemic seizures, but with hyperammonemic symptoms, vomiting, hyperventilation, and lethargy progressing to coma. The most common of the urea cycle defects is OTCD (ornithine transcarbamylase deficiency). This x-linked condition is usually lethal in males, with acute presentation and fatal outcome occurring in the immediate neonatal period. Females express the condition with varying degrees of severity. The first episode can appear at any age from infancy to adulthood. Thus, the patients whom you will meet in the emergency department with OTCD will be females almost exclusively. They often have a prior history of dietary protein aversion. They typically have an immediate history of a febrile illness with vomiting. This is another congenital defect with frequency now known to be similar to phenylketonuria. OTCD very likely accounted for many of the cases of Reye syndrome during the 1970's, and the term "metabolic Reye syndrome" is sometimes used currently to denote a hyperammonemic crisis due to a urea cycle defect, as well as denoting the hypoglycemic crisis occurring with MCAD of the preceding scenario.

6. **Ketoadicosis Due to Overproduction/Underutilization of the Ketones of Fasting (The "hyperketosis syndromes").** Some young children have a metabolic defect which results in exaggerated accumulation of ketones at times of fasting. A vicious cycle of vomiting and fasting ketosis can quickly develop and lead to life-threatening ketoacidosis and dehhydratation. In significant contrast to diabetic ketoacidosis, hyperglycemia is characteristically absent. Several metabolic defects have now been identified which can produce this picture. As a group, we commonly know these disorders as the "hyperketosis syndromes". The most common and familiar example is beta ketothiolase deficiency (more appropriately called mitochondrial acetoacetyl CoA thiolase deficiency), and it can be considered the group prototype. The affected infant or child will have repetitive episodes of severe vomiting, often with hematemesis, progressing to ketoacidosis, dehydration, and coma. Seizures characteristically do not occur with these episodes.

C. By way of background for analyzing what can go wrong during the fasting state, we can look briefly at what should happen during normal fasting. The fasting child is long-since post-absorptive; glycogen stores are depleted; the blood sugar has fallen to low normal but is maintained by gluconeogenesis. Insulin secretion stops, activating release of free fatty acids from fat stores. The liver converts some of the free fatty acids to ketones. Both free fatty acids and ketones are available as alternative energy substrates for the limited glucose available. Severe brain injury may occur.

D. Disruptions in the sequence just described can explain what goes wrong in each of our six prototype disorders:

1. **In the insulin-treated diabetic child** who is experiencing an inadvertent fast, the normal fall in circulating insulin does not occur. As a result, free fatty acids are not released, ketones are not produced, glycogenolysis and gluconeogenesis are inhibited, and the brain must compete with muscle for the limited glucose available. Severe brain injury may occur.

2. **In strong contrast to the child with insulin-induced hypoglycemia, a child with ketotic hypoglycemia** has a normal decrease in insulin output as the blood sugar falls during a fast. The absence of insulin leads to release of free fatty acids and brisk ketone production. The blood sugar then falls markedly because of defective gluconeogenesis, but free fatty acids and ketones are available as alternative energy substrates, sparing glucose for utilization by the brain. Brain damage is not commonly seen in this relatively benign condition, even though the condition can be quite stressful on parents, paramedics, and emergency department personnel.

3. **The major abnormality in the young child who ingests alcohol in the fasting state appears to be inhibition of gluconeogenesis.** Insulin levels fall normally and the alternative substrates, free fatty acids and ketones, are produced normally. The condition closely resembles ketotic hypoglycemia and the risk of brain injury is believed to be relatively low.
4. When the infant with MCAD experiences a pathological fast, insulin levels fall in the normal way as the blood sugar falls. Free fatty acids are released normally but are incompletely utilized. Free fatty acid accumulation in liver, muscle, and brain may even be toxic. Ketones are not produced. In the absence of alternative energy substrates, muscle utilization of glucose continues, the blood sugar falls drastically, and the risk of brain injury or fatal outcome is great.

5. When the little girl with OTCD experiences a fast, blood sugar and insulin fall normally, leading to release of free fatty acids and production of ketones. But, as soon as glycogen is depleted and gluconeogenesis is activated, toxic levels of ammonia accumulate because of the inefficient urea cycle.

6. In an infant or child with one of the hyperketosis syndromes, fasting is associated with normal lowering of blood sugar and insulin levels, normal release of fatty acids, and normal initiation of ketone body production from fatty acids. However, there may be excess production of ketone bodies from one of the ketogenic amino acids (isoleucine) as body proteins are catabolized during the fasting state. Further, there is failure of the activating step which in a normal individual would make it possible for muscle to metabolize the ketone bodies for energy production. Thus, pathological accumulation of ketones is the result both of overproduction and underutilization of ketones. A fatal outcome is possible.

E. Recognizing and Treating the Six Disorders

1. Hypoglycemia in an insulin-treated diabetic: The patient is found unresponsive or convulsing and is identified by bracelet or by history giver as diabetic. Accuchek confirms a very low blood sugar. The urine tests negative for ketones. Glucagon 1.0mg (or 0.02mg/kg if pre-school age child) can be given by EMT. Glucose 25%, 1.0cc/kg IV or glucose 50%, 0.5cc/kg IV will usually produce a faster response than glucagon. Follow with Accuchek sugars every 30 minutes until the patient is responding and is willing and able to eat. Admit for continuous IV glucose if necessary.

Note: Glucagon is rational and effective in this situation because glycogen stores are generous. This will not be the case in the remaining five disorders.

Glucagon dosages need not always be precise, and the full 1.0mg dose can be given to any patient of school age or older. But high dosage of glucagon to a small child might produce vomiting, which could delay getting the patient back on an oral intake. This consideration makes it advantageous, in treating preschool age children, to tailor the glucagon dosage fairly closely to the weight.

2. A child with ketotic hypoglycemia:
The child is unresponsive or convulsing, and is noted to be small for age; the history giver denies diabetes and indicates that recent meals have been missed because of an intercurrent illness. Accuchek confirms an abnormally low blood sugar. The urine (probably obtained after treatment has been initiated) shows very strong ketones.

Treat with 10% glucose IV, 4cc/kg/hour. This could be preceded by the same bolus of 25% or 50% glucose used in treating insulin-induced hypoglycemia. Glucagon would be ineffective because of depleted glycogen stores. Hospitalization is appropriate.

3. A toddler with alcohol-induced hypoglycemia: The child was found unresponsive or convulsing by the parents. There is no history of diabetes or any acute antecedent illness. If asked, the parents may admit that the child was up and around before they were and the last meal may have been the evening before. Blood sugar is very low by Accuchek. Alcohol may be noted on the child's breath, or, if the diagnosis of alcohol ingestion is thought of, a blood alcohol level would be found elevated.

Treatment is identical to ketotic hypoglycemia. Glucagon is not recommended because of depleted glycogen stores. Hospitalization is advisable.

4. The infant with hypoglycemia due to MCAD: The infant was found, unresponsive or convulsing, many hours following the last feeding, or food intake has been curtailed by a vomiting illness. Hepatomegaly is noted on the physical exam. The blood sugar is markedly low by Accuchek. The urine tests negative for ketones (discovery probably made after treatment has been initiated). Liver enzymes and blood uric acid are elevated. A urine organic acid study (obtained acutely but reported several days later) shows increased medium-chain dicarboxylic acids. Blood acylcarnitine profile (obtained acutely but reported several days later) is pathognomonic for MCAD.

The presumptive diagnosis of MCAD is based on the low blood sugar and the absent urinary ketones (“hypoketotic hypoglycemia”), coupled with the hepatomegaly, elevated liver enzymes, and hyperuricemia.

Treatment consists of 10% glucose IV at a rate of 4cc/kg/hour, until regular feedings can be resumed. This could be preceded by the same IV bolus of 25% or 50% glucose used to treat the insulin-induced hypoglycemia.

Glucagon is ineffective because of depleted glycogen stores.

Because carnitine depletion may occur with the MCAD crisis, L-carnitine, 50-100mg/kg/day in two divided doses is given IV or orally.
Hospitalization is indicated.

5. **The little girl with hyperammonemia due to OTCD:** She arrives in the emergency department obtunded and hyperventilating. The transporting EMTs have established that the blood sugar is normal. The history giver indicates that the child has always been a poor eater, frequently rejecting milk, eggs and meat. For two days, she has had a febrile illness with vomiting and today has refused all intake except a few sips of 7-Up. Today, she has become confused and combative with family members.

She now responds only to painful stimuli; the neck is arched; there are a few repetitive slow random movements of the extremities; the pupils are dilated and react sluggishly. Vital signs are normal except that the respirations are 40/minute.

WBC, chemistry profile, CSF, and chest x-ray are normal.

A stat arterial ammonia is markedly elevated.

(Blood amino acids and urine orotic acid are obtained acutely and reported several days later: blood glutamine, blood alanine, and urine orotic acid are all elevated.)

Minimally, treatment will consist of 10% glucose IV at a rate of 4cc/kg/hour. If the patient's condition is severe, this can be increased to glucose 20% by central line with low-dose insulin as needed to keep the blood sugar less than 140. (The glucose-insulin combination has the effect of inhibiting gluconeogenesis, which is the source of the ammonia.) Buphenyl® (sodium phenylbutyrate) is effective in trapping nitrogen products and reducing ammonia production. It is given in a dosage of 500mg/kg/day in three divided doses if the patient weighs less than 20kg, or for patients larger than 20kg, the dose is 10gm/m²/day. Administration is by nasogastric tube. Consider intubation with a cuffed endotracheal tube. Hospitalization is essential and the dialysis team should be alerted as soon as the diagnosis of OTCD is suspected.

6. **The infant or child with hyperketosis:** The patient has probably progressed in a matter of hours from apparent good health, to progressively worsening vomiting, to serious illness with dehydration, severe (and paradoxical) metabolic acidosis, and severe ketosis without hyperglycemia or hypoglycemia. A history of multiple prior episodes is typical. Blood and urine both test strongly positive for ketones. Blood ammonia is normal or only mildly elevated (a markedly elevated ammonia could suggest propionic, methylmalonic, or isovaleric acidemia rather than a hyperketosis syndrome). A urine organic acid study should be obtained acutely, and will usually demonstrate typical metabolites if beta ketothiolase deficiency is the diagnosis. Initial treatment consists of 10% glucose in dilute NaCl/NaHCO₃ with KCl added after demonstration of urinary output. If the ketoacidosis is severe and unrelenting, glucose 20% with low-dose insulin can be used as in OTC deficiency.

Hospitalization is indicated.

**F. Practical Summary Points**

It is typical for these cases to present during the morning hours, with an abnormal antecedent feeding history.

When the blood sugar is low, check urine ketones. Absent ketones imply a potentially serious cause for the hypoglycemia, either hyperinsulinism or a fatty acid oxidation defect. Low blood sugar associated with strong urinary ketones suggests the common and relatively benign diagnosis of ketotic hypoglycemia.

When the blood sugar is normal, check a blood ammonia. When ammonia is elevated, check a urine orotic acid and blood amino acids (obtain these specimens acutely, but they will not be reported stat).

Obtain a spot urine acutely for all of these cases, for ketones, organic acids, and orotic acid as indicated.

Glucagon is indicated only for insulin-induced hypoglycemia and is contraindicated in each of the other scenarios discussed.

25-50% glucose IV may produce a quicker response than glucagon IM in insulin-induced hypoglycemia.

The “D10 rescue” (10% glucose in dilute saline 4 cc/kg/hour IV) is appropriate initial therapy for ketotic hypoglycemia, alcohol-induced hypoglycemia, the hypoketotic hypoglycemia of fatty acid oxidation defects, and the hyperammonemia of urea cycle defects. 10% glucose with added NaHCO₃ based on severity of the metabolic acidosis is appropriate initial therapy for hyperketosis syndromes.
G. Other Conditions

1. MCAD is a prototype member of a larger group of fatty acid oxidation defects. The others have names such as VLCAD, LCHAD, CPT I and CPT II. All can present acutely in the emergency department as hypoketotic hypoglycemia, and the initial stabilizing treatment is identical. Differentiation among the fatty acid oxidation defects can be done in the hospital after stabilization.

2. In addition to OTCD, there are several more congenital urea cycle defects. Their common denominator is hyperammonemia at times of acute catabolic stress. Stabilize them in the emergency department and further differentiation can be carried out after admission.

3. Children with a variety of congenital organic acidemias are also highly intolerant of fasting. These diseases include maple syrup urine disease (branched-chain ketoaciduria), isovaleric acidemia (odor of sweaty feet syndrome), propionic acidemia and methylmalonic acidemia, and glutaric acidemia.

4. Initial treatment for all of these can be 10% glucose at a rate of 4cc/kg/hour with added NaHCO₃ as may be indicated for metabolic acidosis. Patients who have been previously diagnosed with any of these conditions, and again get into trouble, will probably arrive in the emergency department with a letter of introduction detailing the diagnosis and the recommended emergency treatment, as well as a telephone number for the metabolism specialist following the child.

H. References


Slides

PEDIATRIC EMERGENCIES DUE TO FASTING INTOLERANCE

OCCUR IN:

- Insulin-Treated Diabetes Mellitus
- Ketotic Hypoglycemia
- Ethanol Ingestion
- Fatty Acid Oxidation Defects (MCAD)
- Urea Cycle Defects (OTCD)

THE NORMAL FASTING STATE

1. Blood sugar falls; insulin falls.
2. Free fatty acids are released; ketones are produced.
3. Free fatty acids and ketones are utilized by muscle.
4. Gluconeogenesis converts amino acids to glucose; ammonia is a by-product.
5. Glucose is utilized by brain.
6. Ammonia is detoxified by conversion to urea.

FASTING IN INSULIN-TREATED DIABETES
Blood sugar falls; insulin does not

1. FFA are not released; ketones are not produced.
2. Glycogenolysis and gluconeogenesis are not activated.
3. Brain and muscle compete for the small amount of glucose available. Severe neuronal injury may occur.

FASTING IN A CHILD WITH KETOTIC HYPOGLYCEMIA

1. Blood sugar falls; insulin falls.
2. FFA are released; ketones are produced.
3. Glycogen stores are depleted.
4. Gluconeogenesis is defective.
5. Ketosis develops and blood sugar falls abruptly.
6. Because FFA and ketones are available as alternative substrates, muscle does not compete with brain for glucose utilization.
7. Risk of brain injury is small.

FASTING IN AN INFANT WITH A DEFECT IN FATTY ACID OXIDATION

1. Blood sugar falls; insulin falls.
2. Glycogen stores are depleted; gluconeogenesis continues.
3. FFA are released but incompletely utilized; ketones are not produced.
4. Muscle competes with brain for the limited glucose available.
5. Blood sugar falls drastically; risk of brain injury is great.

ALCOHOL INGESTION IN A FASTING NORMAL CHILD

1. Blood sugar falls; insulin falls.
2. FFA are released; ketones are produced.
3. Glycogen stores are depleted.
4. Gluconeogenesis is impeded.
5. Ketosis develops and blood sugar falls abruptly.
6. Because FFA and ketones are available as alternative substrates, muscle does not compete with brain for glucose utilization.
7. Risk of brain injury is probably small.

FASTING IN A CHILD WITH A UREA CYCLE DEFECT

1. Blood sugar falls normally; insulin levels fall normally.
2. FFA are released and ketones are produced.
3. Glycogen is depleted; gluconeogenesis is activated with secondary ammonia production.
4. Conversion of ammonia to urea is defective and ammonia intoxication results.

DIAGNOSIS AND TREATMENT: HYPOGLYCEMIA IN AN INSULIN-TREATED DIABETIC

History: Known diabetic, on insulin, not eating
P.E.: Unresponsive or convulsing
Lab: Fingerstick blood sugar <<60
DIAGNOSIS AND TREATMENT: KETOTIC HYPOGLYCEMIA

History: Pre-school age child, ill, missed supper and/or breakfast
P.E.: Small for age, unresponsive or convulsing
Lab: Fingerstick sugar <<60, urine ketones “black”
Treatment: 10% glucose I.V., 4cc/kg/hour

KEY DETAIL: No glycogen stores, gluconeogenesis defective, glucagon INEFFECTIVE

DIAGNOSIS AND TREATMENT: ALCOHOL-INDUCED HYPOGLYCEMIA

History: Parents sleeping in after party the night before, toddler wandered unsupervised.
P.E.: Unresponsive or convulsing
Lab: Fingerstick blood sugar <<60, blood alcohol elevated
Treatment: 10% glucose I.V., 4cc/kg/hour

KEY DETAIL: No glycogen stores, gluconeogenesis defective, glucagon INEFFECTIVE

DIAGNOSIS AND TREATMENT: INFANT WITH MCAD

History: Previously well infant, unaccustomed long interval between feedings or a febrile illness with vomiting.
P.E.: Unresponsive or convulsing; hepatomegaly.
Lab: Fingerstick blood sugar <<60, urine acetone negative or only slightly positive, liver enzymes elevated, uric acid elevated. Urine contains medium-chain dicarboxylic acids (adipic, suberic, subacic).
Treatment: 10% glucose I.V., 4cc/kg/hour; carnitine 50mg/kg/24 hours I.V.

KEY DETAIL: No glycogen stores, glucagon INEFFECTIVE

DIAGNOSIS AND TREATMENT: THE LITTLE GIRL WITH HYPERAMMONEMIA DUE TO OTCD

History: Prior food aversions; episodic lethargy and vomiting; lethargy and combativeness progressing to coma.
P.E.: Obtunded or unresponsive; dystonic posturing; hyperventilating.
Lab: Blood ammonia >>100; alanine and glutamine elevated; urine orotic acid elevated.
Treatment: 10% glucose I.V., 4cc/kg/hour; Ucephan or phenylbutyrate by NG; dialysis.

**KEY DETAIL:** Hypoglycemia is not a concern. Rationale for I.V. glucose is to minimize gluconeogenesis which is the ammonia source. Glucagon contraindicated.

**SUMMARY POINTS**

1. Occurrence during morning hours is typical
2. Antecedent vomiting and missed meals are common.
3. When blood sugar low, check ketones.
4. When blood sugar not low, check ammonia.
5. Always get a urine (ketones, organic acids, orotic acid).
6. D_{10} is standard initial therapy, except for insulin-induced hypoglycemia.
7. Glucagon is indicated only for insulin-induced hypoglycemia.