METABOLIC EMERGENCIES – PART II

Dana-Teodora Anton-Paduraru
3rd Clinic of Pediatrics, "Gr. T. Popa" University of Medicine and Pharmacy, Iasi

ABSTRACT

Metabolic disorders can manifest especially in the neonatal and infant period by: hypoglycemia, heart failure, primary hyperlactacidemia, liver failure, untreatable convulsions, neurologic damage. The authors present the main manifestations of metabolic emergencies and their emergency treatment.

Keywords: metabolic diseases, emergencies, child

MAIN MANIFESTATIONS OF METABOLIC EMERGENCIES

a. Metabolic acidosis + severe ketosis

Severe ketosis in newborn or infants is the key to the diagnosis for organic aciduria. The most frequent organic acidurias are: propionic and methyl malonic aciduria, multiple carboxylase deficiency, isovaleric aciduria, 3-oxotiolase deficiency.

Routine laboratory tests reveal: low pH, low bicarbonate level, increase in the anionic deficiency, low urine pH.

Hyperchloremic acidosis and anion deficiency determine intestinal loss or renal tubular acidosis. The spectrometric analysis of organic acids is essential for the differential diagnosis.

Metabolic acidosis can be caused by the accumulation of carboxylic acid (for example: lactic acidemia, pyroglutamic aciduria) or by severe ketoacidosis, in which acetoacetic acid and 3-hydroxibutiric acid accumulate in the blood. These are classic metabolic emergencies (5,9,10).

Severe ketosis and metabolic ketoacidosis are signs of organic acidurias. The initial episode can debut with vomiting, anorexia and lethargy and progresses fast to severe acidosis, dehydration, coma and apnea. In the absence of intubation and assisted ventilation, the infant deceases.

Infants with sepsis can be acidotic, but they do not have ketosis. A septic infant with massive ketonuria must be investigated and treated for organic aciduria. Laboratory tests indicate severe acidosis: pH = 6.9-7.2; the bicarbonate level under 5 mEq/l, urine pH under 5.5 (5,9).

In the organic aciduria acute crisis, the level of lactic acid in the blood is very high and can contribute to acidosis. The following may also be present: hypoglycaemia, hypocalcemia, hyperammonemia. Hematologic examination: neutropenia, thrombocytopenia and sometimes anemia. The maple syrup urine disease can appear as a metabolic emergency, but acidosis is mild/absent.

Carbohydrate metabolism disorders, especially glucose-6-phosphatasa von Gierke deficit as well as fructose-6-diphosphatasa deficiency and glycogen synthase deficiency can have high levels of ketone bodies in the blood. However, it is rarely an acute acidotic metabolic emergency, hypoglycaemia being more frequent (4).

b. Lactic acidemia + mitochondrial disease

Inborn anomalies characterised by lactic acidemia are divided into two categories:

– anomalies of gluconeogenesis;

– oxidation defects.

Lactic acidemias are a group of conditions of pyruvate metabolism. The accumulation of pyruvate does not lead to important increases in the pyruvate concentration, but to its conversion into lactate and alanine.

The genetic causes of lactic acidemia are represented by gluconeogenesis and oxidation defects.

Corresponding author:
Dana-Teodora Anton-Paduraru, „Gr. T. Popa" University of Medicine and Pharmacy, 16 Universitatii St., Iasi
E-mail: antondana66@yahoo.com

Their differentiation is useful in determining the optimum treatment. Inborn metabolic diseases producing secondary lactic acidemia include: propionic and methyl-malonic acidemia, isovaleric aciduria, 3-hydroxi-3-methilglutamic aciduria, pyroglutamic aciduria. An unusual cause for lactic acidosis is D-lactic acidemia determined by the absorption of the D-lactic acid produced by intestinal bacteria. Patients suffer from malabsorption or short bowel syndrome, metabolic acidosis and massive lactic aciduria (2,4,10).

c. Hypoglycemia

Hypoglycemia must be immediately recognized and efficiently treated in order to prevent brain destruction.

The metabolic causes of hypoglycaemia must be elucidated based on the evaluation of the response to fasting and the determination of free fatty acids, acetoacetate and 3-hydroxi-butirate in the blood. These enable the differentiation between ketotic hypoglycemia in carbohydrate metabolism diseases and hypoketotic hypoglycemia, which – in the absence of hyperinsulinemia – includes fatty acid oxidation disorders.

Acute hypoglycemia is the manifestation of many diseases. Often, the acute episode can be fatal. Classic symptoms include sweat, paleness, irritability, quivers, but convulsions and coma can also be initial manifestations, especially in newborn. Cephalalgia, lethargy, psychosis, behavioural changes can be noticed in older children, while apnea, tachypnea, cyanosis and hypothermia can emerge in newborn. Surprisingly, patients with the von Gierke disease and glycogen synthesis deficiency have hypoglycaemia without showing symptoms.

Hypoglycemia after a short fasting period signifies a carbohydrate metabolism disease, and after a long fasting period suggests fatty acid disorder. 6-8 hours of fasting lead to hypoglycaemia in patients with glycogenesis type I or glycogen synthase deficiency (1,5,9).

1. Ketotic hypoglycemia

Classically, the syndrome known as "ketotic hypoglycemia" manifests symptomatic hypoglycaemia in the morning after a long fast, often precipitated by an intercurrent disorder. During hypoglycemia, ketone bodies are present in the urine, and the concentration of acetoacetate and 3-hydroxibutirate in the blood is high. In the physical examination, patients can be short and with diminished subcutaneous cell tissue and can have a history of low birth weight.

The two diseases in which ketotic hypoglycaemia is found are:

– glycogen synthase deficiency;

– succinyl-CoA 3-oxoacid CoA-transferase (4,10).

2. Hypoglycemia in carbohydrate metabolism disorders

Patients with glycogenosis type III have low blood concentrations of alanine, hepatomegaly, and do not respond to glucagon after fasting.

Patients with glycogenosis type I or von Gierke disease have high concentrations of alanine. Hypoglycemia appears early and is recurrent. Lactate concentrations are high and ketonuria is frequent.

Patients with gluconeogenesis disorders such as glycerol-kinase deficiency, pyruvate-carboxylase deficiency, pyruvate-carboxykinase deficiency or fructose-1,6-diphosphatase deficiency tend to have high concentrations of alanine and lactate in their blood (5,7).

3. Hypoglycemia in glycogen synthase deficiency

The glycogen synthase deficiency is a rare cause for hypoglycemia. Patients show hypoglycemia a jeun, usually without acidosis, but with high concentrations of acetoacetate and 3-hydroxibutirate and ketonuria. During hypoglycemia, alanine and lactate concentrations are low, but feeding or a glucose tolerance test lead to hyperglycemia and high lactate concentrations in the blood (5,7).

4. Hypoglycemia in fatty acid oxidation disorders

Hypoketotic hypoglycaemia means a fatty acid oxidation disorder. The absence of ketone bodies in the urine during hypoglycemia is a key element. The sudden death syndrome is another form of presentation, and some of the patients show myopathy or cardiomyopathy.

The MCAD (medium-chain-acyl-CoA dehydrogenase) deficiency is the most frequent of these disorders (5,7).

d. Hyperammoniemia

High concentrations of ammonia appear in different inborn metabolic diseases: urea cycle disorders, organic acidurias and fatty acid oxidation disorders.

Classically, the urea cycle disorders debut with a neonatal or potentially lethal coma. The first step in evaluating a patient, particularly an infant, in a coma, is to measure the ammonia concentration in the blood. The following step is the quantification of the serum concentration of bicarbonate, sodium, chloride and the deficiency of anions and ketone bodies in the urine (4).

Acidosis accompanied by severe ketosis signifies organic aciduria (example: propionic aciduria, methyl-malonic aciduria and isovaleric aciduria) or carboxylase deficiency.

Hyperammoniemic coma in the urea cycle defects can lead to hypoxia and lactic acidosis.

The final diagnosis of the urea cycle anomalies is based on the quantitative analysis of amino acid concentrations in the blood and urine.

The differential diagnosis of hyperammoniemia includes the HHH (hyperammoniemia-hyperornithinemia-homocitrullinuria) syndrome characterized by deficiency of the ornithine transporter to the mitochondrial membrane and lysinuric protein intolerance.

e. Acute neurologic and psychiatric manifestations

The acute or recurrent coma, ataxia or abnormal behaviour attacks are major characteristics especially of the inborn metabolic diseases with tardy debut. Certain significant metabolic manifestations such as acidosis or ketosis can be moderate or transient. On the other hand, in the advanced stage of organic dysfunction, many laboratory anomalies (metabolic acidosis, hyperlactic acidemia, hyperammoniemia, signs of liver failure) can be secondary consequences of hemodynamic shock and multisystem failure (4,10).

Acute metabolic brain edema must be recognized and treated early in order to prevent herniation and decease. It is found especially in acute hyperammoniemias (ornithine transcarbamylase deficiency) and in the maple syrup urine disease.

Acute hemiplegia can be a symptom found in organic acidurias, particularly propionic and methyl-malonic aciduria, as well as in phosphoglycerate-kinase deficiency and mitochondriopathies.

An acute debut with extrapyramidal signs during a non-specific intercurrent sickness, minor surgical trauma or immunization can be interpreted erroneously as encephalitis, because it can be a sign of severe metabolic disease.

In glutaric aciduria type I, acute encephalopathic crisis appears typically between 6 and 18 months. Metabolic shock can be noticed in some metabolic diseases: homocystinuria, congenital glycosylation diseases, urea cycle anomalies, Menkes and Fabry disease.

The classical brain shock as well as cardiovascular accidents can be caused by metabolic diseases (homocystinuria, Fabry disease).

Acute ataxia or the psychiatric manifestations can be signs of organic acidurias or of the maple syrup urine disease with tardy debut.

The urea cycle disorders can include acute ataxia or psychiatric symptoms such as hallucinations, delirium, aggressiveness, anxiety, dizziness, schizophrenia-like symptoms.

Mitochondrial diseases manifest at the level of the energy-consuming structures of the central nervous system, such as basal ganglions, capillary and brain endothelium.

Acute ataxia associated with peripheral neuropathy is frequently found in patients with pyruvate dehydrogenase deficiency. The moderate/important increase in the lactate, with a normal lactate/pyruvate ratio and the absence of ketosis support the diagnosis. In exchange, ataxia associated with a high lactate/pyruvate ratio suggests multiple carboxylase deficiency.

Certain inborn metabolic diseases such as the HARTNUP diseases can show acute recurrent ataxia. Some typical traditional symptoms (cutaneous rash, pellagra, sun intolerance) can impose testing urine amino acids confirming the diagnosis (4,10).

Acute intermittent porphyria and hereditary coproporphyria is characterised by recurrent attacks of vomiting, abdominal pain, non-specific neuropathy and psychiatric symptoms. Psychiatric symptoms can also be present in the cell methylation disorders such as methyl-tetrahydrofolate reductase deficiency. Other neurologic symptoms include shock, convulsion and myelopathy episodes.

EMERGENCY TREATMENT IN INBORN METABOLIC DISEASES

The correct and timely treatment of the initial disease episode and subsequently during the episodes triggered by the failure to observe the diel or by recurrent infections is the most important factor determining the evolution of the inborn metabolic diseases running the risk of acute metabolic decompensation.

In the diseases running the risk of acute metabolic decompensation, the emergency treatment must be initiated even in the absence of a full diagnosis. The administration of a sufficient amount of fluids and electrolytes is compulsory (2).

The energetic needs of infants with inborn metabolic diseases are indicated in Table 1.

In the conditions in which the symptoms are due to an "acute intoxication", the treatment is based on the quick decrease of toxic molecules.

In amino acid catabolism diseases, such as the maple syrup urine disease, classical organic acidurias or urea cycle defects, the toxic compounds can come both from exogenous and endogenous

TABLE 1. *Necessary energy for infants with inborn metabolic diseases*

Disease	Necessary energy
Diseases that need anabolism: – organic acidurias, maple syrup urine diseases, urea cycle disorders	– 60-100 kcal/kg/day; – 15-20 g glucose/kg/day – 2 g lipids/kg/day – insulin: 0.05 UI/kg/hour (the dose will be adjusted depending on the glycemia level)
Diseases that need glucose stabilization (low fasting tolerance): – fatty acid oxidation defects, glycogen storage diseases type I, gluconeogenesis disorders, galactosemia, fructose intolerance, tyrosinemia	– glucose: 7-10 mg/kg/ min (approximately 10 g/kg/day)
Perturbed energy metabolism diseases: – pyruvate-dehydrogenase deficiency – electron transport disorders	– decrease in the glucose intake: 2-3 mg/kg/min (approximately 3 g/kg/day) – glucose 10-15 g/kg/day

sources. The major objective of the treatment is to stop the natural protein intake until the end of the crisis, but not for more than 12-48 hours, reverse catabolism and further anabolism.

Emergency therapeutic measures in patients with amino acid catabolism diseases with intercurrent infections and metabolic perturbations (for instance: ketonuria) consist of more frequent meals high in carbohydrates and salt and low intake of natural proteins.

The following detoxifying medication is recommended:

– Carnitine in organic acidurias;

– Benzoate, phenyl acetate and arginine or citrulline in hyperammonemias.

Periodically, the awareness state, food tolerance and therapy tolerance will be monitored.

Mounting a venous catheter is essential, as well as the use of a nasogastric probe (for instance: in the maple syrup urine disease, for the administration of the amino acid mixture).

The calculation of maltodextrin/dextrose, fluids and proteins will consider the ideal calculated weight, not the current weight.

The administration of insulin must begin early, especially in the presence of severe ketose.

Acute severe ketoacidosis episodes need special supportive therapy. Large amounts of glucose, fluids, electrolytes, bicarbonate and carnitine (200 to 300 mg/kg) will be perfused.

After an initial bolus of 20 ml/kg Ringer or physiologic serum, 75-150 mEq/l bicarbonate will be administrated intravenously (75 mEq/l in severe ketosis; 150 mEq/l in coma or if the bicarbonate level is under 10 mEq/l) (5,7,9).

Diuresis forced with high amounts of fluids and Furosemide is useful in methyl-malonic aciduria.

In isovaleric aciduria, glycine 500 mg/kg will be administrated for the excretion of isovalerylglycine.

In the maple syrup urine disease, the treatment consists in administrating amino acid mixtures without leucine, isoleucine and valine (2 g/kg).

In metabolic emergencies with hyperammonemia benzoate and phenilacetate will be administrated intravenously. Zofran 0.15 mg/kg is administrated intravenously to control the vomiting accompanying hyperammoniemia. If ammoniemia exceeds 600 μmol/l (100 μg/dl), extracorporeal dialysis is recommended.

In aminoacidopathies (phenylketonuria, homocystinuria and tyrosinemia), the toxic metabolites lead especially to chronic organic destruction and determine metabolic emergencies to a smaller extent. Hepatorenal tyrosinemia can lead to liver failure (5,7,9).

In tyrosinemia type I, Nitisone (NTBC) – a p-hydroxyphenyl-pyruvate dioxygenase inhibitor blocking the genesis of toxic fumaryl-acetoacetate and its derivatives – will be administrated.

In galactosemia or fructose intolerance, in which toxic metabolites derive predominantly from exogenous sources, therapy consists in the elimination of the galactose and fructose intake.

In fatty acid oxidation defects and gluconeogenesis, glucose will be administrated in sufficient amounts to restore and maintain the glycemic level at normal values.

Carnitine supplements in fatty acid oxidation defects is controversial. The long-term management excludes fasting.

In conditions perturbing the energy metabolism (pyruvate-dehydrogenase defects, Krebs cycle disorders etc.), the emergency treatment focuses on the correction of the life-threatening acidosis and lactic acidemia. The correction of metabolic acidosis imposes the administration of a high amount of bicarbonate. Depending on the cause, the level of lactic acidemia can be reduced by dialysis or by dichloroacetate administration.

In the mitochondrial disease, the administration of coenzyme Q10, vitamin E and a B vitamin complex (thiamine, riboflavin, niacin, pyridoxine, biotin, pantothenic acid) is recommended. The presence of carnitine deficiency in the blood or of the high urine excretion of carnitine imposes the administration of L-carnitine (5,7,9).

The last objective of the treatment is to prevent irreversible brain damage. Mannitol will be administrated in treating brain edema, which can improve detoxification by increasing diuresis. High intracranial pressure will be surgically monitored.

In metabolic emergencies, nutrition is very important, enteral nutrition can be useful temporarily in these patients, and full parenteral nutrition is the election method in patients with intestinal intolerance, with high energy needs or with invasive techniques for toxin elimination (3).

Table 2 presents the main treatments for inborn metabolic diseases.

TABLE 2. *Specific treatments for inborn metabolic diseases*

Medication	Dose	Advice
Arginine 10%	210-600 mg/kg i.v.	Urea cycle diseases
Biotin	10 mg p.o./i.v.	Organic aciduria
Carnitine	50-400 mg/kg p.o. /i.v.	Fatty acid deficiencies, organic acidurias
Pyridoxine	100 mg i.v.	Convulsions
Sodium benzoate and/or Phenyl acetate	250 mg i.v.	Urea cycle diseases
Thiamine	25-100 mg i.v.	Maple syrup urine disease, primary lactic acidosis

REFERENCES

1. **Jain A., Aggarwal Rajiv, Jeeva Sankar M., Agarwal Ramesh, Deorari A. şi col.** Hypoglicemia in the newborn. *Indian J Pediatr* 2010; 77: 1137-1142.
2. **Carroll R., Matfin G.** Endocrine and metabolic emergencies: hypocalcemia. Therapeutic Advances in Endocrinology and Metabolism 2010; 1 (1): 29-33.
3. **Chritodoulou J.** Clinical evaluation and emergency management of inborn errors of metabolism presenting in the newborn. *Southeast Asian J Trop Med Public Health* 2003; 34;Suppl 3: 189-197.
4. **Ewing P., Wiebe J.** Evidence-Based Management of Metabolic Emergencies in the Pediatric Emergency Department. *Pediatric Emergency Medicine Practice* 2009; 6 (10): 1-16.
5. **Kwon K., Tsai Virginia.** Metabolic Emergencies. *Emerg Med Clin N Am* 2007; 25: 1041-1060.
6. **Lupea I.** Neonatologie. Editura Dacia, Cluj Napoca 1994; 446-451; 452-454; 466-469.
7. **Miu N.** Hipoglicemia în Popescu Antonia, Miu N. Strategii terapeutice în unele boli metabolice şi digestive la copil. Editura RISOPRINT, Cluj Napoca 1997; 85-102.
8. **Nyhan W.** Metabolic Emergencies in Hoffmann G., Zschoche J., Nyhan W. Inherited Metabolic Diseases. A Clinical Approach. Springer. Verlag Berlin Heidelberg 2010; 25-59.
9. **Spinazze Silvia, Schrijvers D.** Metabolic emergencies. Critical Reviews in Oncology/Hematology 2006; 58(1): 79-89.
10. **Ţurcanu L., Mitrofan Lucia.** Neonatologie. Editura Medicală, Bucureşti 1985; 174-178.
11. **Weiner D.L.** Metabolic emergencies. In: Fleisher G.R., Ludwig S., Henretig F.M. (Eds). Textbook of pediatric emergency medicine, 5th ed, Lippincott, Williams and Wilkins, Philadelphia 2006; 1193.