METABOLIC EMERGENCIES – PART I

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ABSTRACT

Often, patients with metabolic conditions (diseases caused by electrolytic unbalances, endocrine dysfunctions, inborn errors of metabolism) have symptoms similar to other emergencies, particularly as newborns and infants. The authors present the main emergencies: electrolytic unbalances – hypoglycemia, hyponatremia, metabolic acidosis and neonatal hypocalcemia; endocrine dysfunctions – suprarenal insufficiency and neonatal hypopituitarism; inborn metabolic diseases – acidosis, hyperglycemia/ hypoglycemia, hyperammoniemia, clinical symptoms associated to them, and recommended treatment.

Keywords: metabolic diseases, emergencies, child

Patients with metabolic diseases often have symptoms similar to those of other (infectious, neurologic, toxicological) emergencies, particularly as newborns and infants:

- hypoglycemia (example: in hyperinsulinism, glycogen storage diseases, mitochondrial diseases);
- heart failure (example: fatty acid oxidation disorders)
- primary hyperlactacidemia (example: enzyme defects);
- liver failure (example: galactosemia, hereditary fructose intolerance, tyrosinemia type I);
- untreatable convulsions;
- neurologic deterioration (example: maple syrup urine disease, organic aciduria, urea cycle disorders).

The metabolic diseases include:

a. diseases due to electrolytic unbalances;
b. endocrine dysfunctions;
c. inborn metabolic diseases;

a. Diseases due to electrolytic unbalances – emergencies

Hypoglycemia

Hypoglycemia is one of the most frequent metabolic problems, especially in new-born.

The causes for hypoglycemia are many:

- the decrease in the glucose production/ availability: malnutrition, fasting, malabsorption, diarrhea, low glycogen deposits (premature, low birth weight);
- increase in the use of glucose: hyperinsulinemia states (infant coming from a diabetic mother, nesidioblastoma, adenoma/islet cell hyperplasia, Wiedemann-Beckwith syndrome);
- stress (infections, sepsis);
- inborn metabolic diseases;
- hormonal deficits (suprarenal insufficiency, growth hormone deficit, glucagon deficit).
- iatrogenic causes: intoxications (ethanol, propanolol, salicylate), Reye syndrome, treatment of hyperglycemia (1,6,10).

The symptoms of hypoglycemia are divided into two categories:

1. symptoms associated with the activation of the autonomous nervous (adrenergic) system: tachycardia, tachypnea, vomiting.
2. symptoms associated with the decrease in the brain (neuroglycopenic) use of glucose: lack of appetite, lethargy, alteration of mental status, convulsions (3,6,9,10).

In infants, the symptomatology may include hypotonia, hypothermia, exaggerate primitive reflexes and feeding disorders.

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The early detection of hypoglycemia is very important as permanent brain destruction starts shortly afterwards, and hypoglycemia in patients who need resuscitation in Intensive Care is associated with increased mortality.

Acute treatment of hypoglycemia consists of bolus administration of glucose 0.2-1 g/body kg (10% solution in newborn and infants and 25% solution in children). After the bolus, the administration of glucose will continue (mg/kg/ min) to maintain normal homeostasis of glucose (4,6,10).

If hypoglycemia continues, the hyperinsulinemic status will be considered and 20-50 μg of Octreotide or Glucagon 0.1-0.2 mg/body kg (maximum 1 g/ body kg) will be administrated subcutaneously. Glucagon is not efficient in patients with losses of the glycogen deposits (for instance, in hereditary storage diseases).

In refractory hypoglycemia, medication therapy with Hydrocortisone 2-3 mg/kg or 25-50 mg/m^2 or ACTH 4U/ kg will be associated.

Glycemia will be tested every 30-60 minutes until the normalization of glycemia, then every 8-10 hours (7).

Hyponatremia

Less frequent in comparison to hypoglycemia, hyponatremia (sodium values under 125-130 mEq/l) is a frequent disorder in hospitalized children (4).

It may be caused by:

- saline losses following vomiting or diarrhea;
- excessive administration of diuretics;
- suprarenal insufficiency;
- excessive water (syndrome induced by infections due to inappropriate secretion of antidiuretic hormone, nephritic syndrome, cirrhosis).

In infants, hyponatremia is frequent due to excessive gastrointestinal losses following vomiting or prolonged diarrhea or due to inappropriate dilutions of formula (3).

The clinical manifestations of hyponatremia include: alteration of the mental status, lethargy, vomiting, diarrhea, convulsions and circulatory collapse (4).

The treatment consists first of all in the treatment of the cause that determined hyponatremia. Aggressive treatment with 3% hypertonic saline solution (514 ml/kg) will be initiated only when important symptoms such as convulsions and coma are present. An amount of 5 ml/ kg administrated during 10-15 minutes increases the natremia level by approximately 5 mEq/l.

The sodium deficit will be calculated according to the formula:

$$\text{Necessary } Na^+ \text{ (mEq)} = 0.6 \times \text{weight (kg)} \times (\text{normal } Na^+ - \text{measured } Na^+).$$

After the symptoms are corrected, the purpose of the treatment is to slowly increase the Na^+ level by 0.5 mEq/l (maximum 12 mEq/l/day) with NaCl 0.9%.

In the cases of antidiuretic hormone deficit, fluids will be restricted (2/3 of the necessary amount) and Furosemide will be administrated 1-2 mg/body kg.

In the newborn with untreatable convulsions of unspecified etiology, 100 mg of Pyridoxine will be administrated intravenously.

Metabolic acidosis

Metabolic acidosis appears by means of 3 major mechanisms:

1. loss of bicarbonate through the gastrointestinal or renal tract;
2. surplus of acids due to endogenous production or from exogenous sources;
3. low excretion of acid by the kidneys.

The causes for metabolic acidosis due to the anionic deficit are:

- in case of a normal anionic deficit (12±4): gastroenteritis, renal tubular acidosis, suprarenal insufficiency.
- in the case of high anionic deficit (over 16): methanol, paraldehyde, salicylates and ethylene glycol intoxications, uremia, lactic acidosis;
- inborn diseases of the metabolism of carbohydrates, amino acids and fatty acids;
- chronic kidney failure;
- starvation (5,11).

The clinical manifestations of metabolic acidosis are unspecified and include the alteration of the mental status, vomiting, respiratory distress. An important warning sign, especially in infants, is tachypnea – a compensatory mechanism determining an alkalotic respiratory response.

The treatment focuses on

- electrolytic rebalancing;
- therapy specific to the cause of metabolic acidosis.

The use of bicarbonate is controversial. It is recommended only in hereditary diseases or in diseases in which acidosis determined important arrhythmia and hemodynamic instability. The bicarbonate improves the heart function and blood pressure, but its benefits are only transient (3,6,10).

The bicarbonate treatment can be harmful, because it deviates the oxygen-hemoglobine dissociation curve to the left and can worsen tissue hypoxia, particularly in hypovolemic patients. In addition, it can determine hypernatremia and hypokalemia. In newborn, perfusion with Albumine 5% is less efficient in comparison to the administration of bicarbonate for the correction of metabolic acidosis.

Neonatal hypocalcemia

The causes for early hypocalcemia (values of total calcium under 7 mg% and of ionic calcium under 3-3.5 mg%) are: prematurity, neonatal asphyxia, infections, phototherapy, exchange transfusion, pregnancy toxemia, hyperparathyroidism, gestational diabetes (2).

The main clinical manifestation is represented by apnea crises. Other manifestations are: hyperexcitability, tremor, hypotonia, cyanosis crises, convulsions.

The treatment consists in the endovenous administration of a 10% calcium gluconate solution until the disappearance of the symptomatology. During the calcium perfusion, the heart rate will be monitored (risk of bradycardia) (4). Subsequently calcium will be administrated orally, potentially together with vitamin D.

b. Endocrine dysfunctions – emergencies

Suprarenal insufficiency is due either to the primary suprarenal disease or secondary to pituitary suppression.

Congenital suprarenal hyperplasia is an important cause for primary suprarenal insufficiency during neonatal period, while the Addison disease is more frequent in children and teenagers, as well as secondary suprarenal hyperplasia.

The clinical expression of suprarenal hyperplasia (21-hydroxylasis deficit) is the consequence of hyperandrogenism, with or without associated mineralocorticoid deficit (4).

Congenital/ acquired acute suprarenal insufficiency is associated with hyponatremia, hyperkalemia and hypoglycemia (4).

In the disease forms that imply salt loss, the patient's life is threatened by two major risks:

- the cardiotoxic effect of hyperkalemia;
- hypovolemic collapse.

In these forms, the treatment consists in:

- the treatment of the acute dehydration episode: hydro-electrolytic rebalancing under the continuous control of the clinical hydration state and of serum and urinary electrolytes, the i.v. administration of Hydrocortisone hemisuccinate and Mincortid 2-4 mg/day;
- maintenance treatment: association of glucocorticoids (Hydrocortisone hemisuccinate 25-50 mg/m^2 or Dexamethasone 0.1-0.2 mg/kg) and mineralocorticoids (Flydrocortisone 0.1 mg per os daily) (4,6,10).

Usually, hyperkalemia is corrected based on hydro-electrolytic rebalancing and corticotherapy and rarely needs individual correction, as the newborn can tolerate higher levels of potassium in comparison to children and adults.

Neonatal hypopituitary crisis

Clinical symptoms appear within the first 12 hours of life and are represented by cyanosis, lethargy, convulsions and circulatory collapse accompanied by severe hypoglycemia. The surviving cases have prolonged jaundice.

Pituitary hormonal deficit will be suspected in cases with persistent hypoglycemia accompanied by hypotension and – in males – by micropenis and small testicles.

The emergency treatment consists in the administration of Hydrocortisone and glucose endovenously, and in case of severe bradycardia, thyroid hormones will be administrated (6,10).

c. Inborn metabolic diseases – emergencies

Classically, the inborn metabolic diseases (organic acidurias, urea cycle disorders, maple syrup urine disease, non-ketotic hyperglycemia, diseases related to the fatty acid oxidation etc.) debut after a free period of apparent health that can last for a few hours (12-48 hours), even a few months (6-8 months) followed by life-threatening events (recurrent metabolic decompensation episodes often accompanied by infections) (3,8,10).

The most frequent clinical manifestations of metabolic emergencies in inborn metabolic diseases are: recurrent vomiting, neurologic disorders (convulsions, hypotonia, coma) and hypoglycemia. The presence of the following symptoms can indicate the presence of an inborn metabolic disease:

- acidosis and hyperglycemia indicate the presence of organic acidemia;
- hyperammoniemia and alkalosis are characteristic to urea cycle disorders;
- hypoglycemia is found in fatty acid oxidation diseases;
- high levels of lactate in the absence of heart diseases, shock of hypoxemia are significant for organic acidemias and even hyperam-

moniemias, as well as for lactic acidemia in mitochondrial disease;
- the dinitrophenyl-hydrazine test is positive in all conditions in which ketone bodies are present in large amounts in the urine. In practice, it is useful for the diagnosis of the maple syrup urine disease (MSUD) (3,6,8,10,11).
- the presence of reducing substances in urine can be the first indicator in galactosemia.

The initial clinical manifestations of emergencies in inborn metabolic diseases are vomiting, anorexia and food refusal. These can be followed by acidotic breath, quick progression to lethargy and convulsions or coma. Certain cases can evolve to apnea and decease in the absence of intubation and assisted ventilation.

Initially, the laboratory evaluation includes only routine tests for the highlighting of acidosis/ alkalosis, hyperammonemia, ketosis, hypoglycemia or lactic acidemia, and subsequently tests specific to the suspected disease.

MANIFESTATIONS IN NEWBORN

During the neonatal period, metabolic diseases are manifested by life-threatening events representing medical emergencies.

Usually, these newborn are apparently normal upon birth. The warning signs suggesting the presence of a metabolic disease in new-born are:
- vomiting: this often leads to the pyloric stenosis/duodenal obstruction. But, an acidotic patient suspected of pyloric stenosis must be investigated related to a metabolic disease.
- acute acidosis;
- severe ketosis;
- coagulopathies;
- deep coma;
- convulsions, especially myoclonyas;
- unusual smell;
- extensive dermatosis;
- chronic hiccup;
- family history of early decease (3,6,8,10,11).

The picture of life-threatening events in newborn often raises the suspicion of sepsis. But in a newborn coming from a pregnancy without complications, sepsis is unusual, and a potential metabolic emergency must be considered and investigated in parallel.

MANIFESTATIONS IN INFANTS

Infants can manifest the picture of a life-threatening event, just like in the neonatal period, or can manifest the failure of growth. Such an infant is difficultly fed and can manifest frequent vomiting, but the metabolic crisis is excluded until the emergence of an intercurrent infection or until the passage from natural feeding to cow milk feeding. The etiology is the same: organic aciduria, hyperammoniemia, hepatorenal tyrosinosis, fructose intolerance (6,8,10).

Usually, the fatty acid oxidation diseases manifest between the ages of 7 and 12 months, when the infant sleeps more, and manifests anorexia and vomiting. Classically, they manifest convulsions/ coma/frequent heart arrhythmia, hypoglycemia and hypocetosis.

Muscle tonus is affected in different metabolic diseases: organic acidurias, fatty acid oxidation diseases.

Infants suspected of Reyes syndrome are candidates to the inborn metabolic disease diagnosis. Many of them suffer from acyl-coenzyme A dehydrogenase deficiency or ornithine-transcarbamylase deficiency (6,8,10).

MANIFESTATIONS IN OLDER CHILDREN

Any of the metabolic diseases debuting in the infant period can lead to repeated emergency metabolic attacks at any age, even under treatment. The forms with a tardy debut are more frequently found in urea cycle disorders, and ammoniemia must be determined in any patient with awareness disorders and unexplained coma.

Fatty acid oxidation disorders can have a tardy debut if the patient has not refused feeding for a long time, which could have determined fat oxidation. Therefore, acyl-coenzyme A dehydrogenase deficiency can originally appear as a fatal episode of hypoketosis hypoglycemia. Other diseases of fatty acid oxidation can appear tardily, with acute rhabdomyolysis and heart arrhythmia. These patients have high levels of creatine kinase and uric acid during their crisis. Others can manifest acute heart failure, as a consequence of repeated cardiomyopathies and of the depletion of carnitine deposits.

Mitochondrial diseases can debut at any age, but rather in childhood than in adulthood. In their first episode, the patient can manifest a coma with lactic acidosis and ketoacidosis.

The MELAS disease debuts by shock or a shock-like episode. Such episodes are also present in propionic and methylmalonic aciduria, ornithine-transcarbamylase deficiency and congenital glycolysis diseases (8).

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