



Case Report

DOI: <http://dx.doi.org/10.22192/ijcrms.2017.03.01.003>

Recurrent severe metabolic acidosis in prematurely born infant – Case Report

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Abstract

Metabolic acidosis (MA) is not a disease but rather a biochemical abnormality due to disorder of the acid-alkaline homeostasis. Untreated, the severe MA is urgent condition for patients at any age and can lead to myocardial depression, convulsions, shock, and multiorgan failure. Common causes of MA in the neonates are sepsis, necrotizing enterocolitis, hypothermia, asphyxia, intracranial haemorrhages, persistent ductus arteriosus, shock, and drugs. Rare causes are inborn errors of metabolism, renal tubular acidosis, increased loss of bicarbonates through the unstable stools due to malabsorption, starvation.

We present a case of severe recurrent MA in a newborn of risk pregnancy (43-aged mother, in vitro conception), born prematurely with symmetric intrauterine growth restriction. The early neonatal period was compromised by necrotizing enterocolitis with small intestine perforation. Surgery intervention was performed on the 12th postnatal day (partial small intestine resection and outputting of anus praeter iliacus). Congenital heart anomaly (atrial septal defect) as an accompanying disease was presented by cardiac failure in the first few weeks. The clinical course was aggravated additionally by toxic liver injury with cholestasis due to prolonged parenteral nutrition and difficulties in enteral nutrition. The incidents of decompensate MA came forward after 6th postnatal (41st postconceptual) week and high doses of bicarbonate were needed for adequate correction. These cases of MA were interpreted as result of high bicarbonate losses by diarrheic stools through the anus iliacus. The acid-alkaline balance was stabilized by administering of regular peroral intake of bicarbonate up to definitively surgery recovery of the normal bowel passage at the age of 6 months.

Keywords: acid-alkaline homeostasis, newborn, prematurity.

1. Background

Acid-base balance is a vital dynamic index of a newborn welfare, and it is best assessed by blood gas analysis. The normal plasma pH values are from 7:36 to 7:45. Metabolic acidosis is a disorder of the acid-base homeostasis that occurs when pH is under 7.26. When pH is over 7.26, and the carbon dioxide is high, there is a respiratory acidosis, but if carbon dioxide is in normal or low values, there is a metabolic acidosis.

MA is very common in newborns and can be observed in a variety of disorders such as infection, severe catabolic conditions, tissue hypoxia and dehydration. Therefore, establishing the correct rate could be difficult. (Watkinson M, 2005)

Causes of MA in the neonatal period can be divided into two groups. Common diseases accompanied by metabolic acidosis include: sepsis, necrotizing enterocolitis, hypothermia, asphyxia, patent ductus arteriosus, shock, drugs and peri- and intraventricular hemorrhage. Rare causes can be congenital metabolic disease, renal tubular acidosis, late acidosis in preterm babies, increased loss of bicarbonate in short bowel syndrome, starvation. (Friedlich PS, Seri I, 2015; Brodsky D, Doherty EG, 2014)

The limited ability to maintain and regulate the acid-base balance is a characteristic clinical feature in the neonatal period. Physiologically, premature infants often suffer from mild to MA with normal anion gap as a consequence of low renal bicarbonate retention of immature kidneys. (Friedlich PS, Seri I, 2015) In the neonatal period MA can be classified by normal or increased anion gap, which represents the difference between measured serum or plasma cations and anions : $[(Na^+) + [K^+)] - ([Cl^-] + [HCO_3^-])$. (Gomella TL, 2013) Severe acidosis in this specific period may cause increased pulmonary vascular resistance, inhibited surfactant synthesis, myocardial or diaphragmatic contractility damage and impaired kidney excretion.

2. Case Report

We present a clinical case of severe MA in the neonatal period. The patient is a preterm baby born from a risk pregnancy of 43-year-old mother (IVF, obesity, varices, fraxiparine therapy) delivered via Cesarean section in 35th gestational week. It was born in depressed condition requiring cardio-respiratory resuscitation.

Due to immaturity and symmetric intrauterine growth restriction the patient was transferred to the Intensive Care Unit. The therapeutic approach included thermal comfort, oxygen, combined empirical antibiotic therapy and parenteral nutrition by central venous catheter.

The clinical condition of the patient deteriorated since 4th-5th postnatal day presenting by syndrome of gastrointestinal dysfunction: beginning with the impossibility of enteral feeding and complicated by development of peritonitis (abdominal bloating, gastric residuals of intestinal contents, abdominal distension, lack of peristalsis). On the 12th postnatal day an emergency surgery was performed, proving perforation of the small intestine and meconium peritonitis. An intestinal section was resected and anus praeter was output.

The general condition was aggravated by diagnosed cardiac malformation – hemodynamically significant atrial septal defect. The clinical picture was extended by heart failure expressed with tachycardia, abnormal vascular permeability, dysalbuminaemia and generalized swelling. Treatment with an ACE inhibitor and loop diuretic was administered.

A liver damage with cholestasis was a severe complication which was etiologically associated with intestinal passage disorder, total parenteral nutrition, late enteral feeding and aggressive medical therapy.

A persistent thrombocytopenia represented a clinical interest. It was interpreted most likely due to bone marrow suppression of infectious genesis or platelet dysfunction.

After hospital stay of a total of 38 days the child was discharged with stable vital signs, drug controlled cardiac function and good food tolerance.

A week later the patient was re-hospitalized in impaired condition, with so called “verdin icterus”, reduced turgor and skin elasticity, expressed consumptive syndrome. The following objective signs were marked: tachypnea, chest retractions, single small wet rales bilaterally. Muffled cardiac tones accompanied by systolic murmur 4/6 degrees on the left were auscultated.

Abdomen allowed palpation and normal peristalsis and passable stoma were presented. Blood samples revealed metabolic imbalance with severe metabolic decompensated acidosis, accompanied by electrolyte imbalance (Table 1). To correct these disorders were needed three consecutive intravenous infusions of Bicarbonate according to Astrup's formula, adequate fluid and calories intakes. Stabilizing of the electrolytic state was finally achieved by blood transfusion. The clinical condition improved. Enteral feeding was restored and the child began to gain weight.

Table 1: Indices of blood gases analyses (heel samples) in the first episode of deterioration

Date / Time	pH	pCO ₂	pO ₂	AB	SB	BE	Therapy
25 Dec 14 / 08:30	6.96	33.4	67.0	8.6	7.5	-23.9/-24.6	NaHCO ₃ , FT*
25 Dec 14 / 15:30	7.11	29.5	65.0	10.3	9.4	-18.9/-20.1	NaHCO ₃ , FT
25 Dec 14 / 22:00	7.2	30.6	56.0	13.0	12.1	-14.7/-16.1	FT
28 Dec 14 / 11:00	7.19	43.5	33.0	17.8	16.5	-11.6/-12.0	NaHCO ₃ , FT
29 Dec 14 / 11:00	7.18	54.6	45.0	22.1	20.5	-8.5/-8.1	BT**

**Fluid therapy, **Blood transfusion*

Second episode of severe metabolic acidosis occurred during the 8th postnatal week – again with a catastrophic deterioration in general condition (waning, respiratory failure with wheezing, severe hypotrophy). Dominant issue

during this period was the cardiac dysfunction accompanied by dyspeptic syndrome, clinically manifested by severe dehydration and decompensated metabolic acidosis (Table 2).

Table 2: Indices of blood gases analyses (heel samples) in the second episode of deterioration

Date / Time	pH	pCO ₂	pO ₂	AB	SB	BE	Therapy
23 Jan 15 / 08:00	6.9	43.3	46.0	***	***	***	FT*
23 Jan 15 / 23:00	6.9	26.4	42.0	***	***	***	NaHCO ₃ , FT
24 Jan 15 / 07:00	7.0	27.0	57.0	7.6	6.7	-23.5/-24.7	NaHCO ₃ , FT
24 Jan 15 / 12:00	7.04	32.6	57.0	9.8	8.8	-21.1/-22.0	FT
24 Jan 15 / 18:00	7.05	36.3	49.0	11.3	10.1	-19.7/-20.5	FT
25 Jan 15 / 07:00	7.06	36.5	52.0	11.6	10.4	-19.2/-20.0	NaHCO ₃ , FT
25 Jan 15 / 17:00	7.28	40.0	45.0	26.0	18.9	-7.5/-8.0	NaHCO ₃ p.o.

**Fluid therapy*

An infectious agent was suspected because of the characteristic hematologic abnormalities (leukocytosis and elevated acute phase proteins). Broad-spectrum antibiotics, parenteral feeding, correction of acidosis with bicarbonate were administered, but acid-base state compensation was not reached. Due to clinical indications

bioproducts were added. Having taken into consideration the recurring episode of metabolic acidosis, oral intake of bicarbonates was prescribed and the acidosis was permanently corrected. Hematological indices returned to normal.

3. Discussion

The rich in symptoms and syndromes clinical presentation with leading significance of repeated metabolic acidosis calls for a wide differential diagnosis, including congenital metabolic diseases, lactate acidosis, renal acidosis, malabsorption syndrome with loss of bicarbonate, starvation. In these nosological units metabolic acidosis is often manifested by nonspecific symptoms: poor feeding, lethargy, hypotension, vomiting, hypothermia, seizures, breathing disorders.

Inborn errors of metabolism (presented by encephalopathy with or without metabolic acidosis, compromised cardiac or liver function, dysmorphic syndromes, non-immune hydrops fetalis) are considered in the first place of the rare causes of metabolic acidosis.

Given the clinical features in our case, the defects in urea cycle, amino acids metabolism and carbohydrate metabolism are noteworthy from the large group of metabolic diseases.

The transient hyperammonemia of the newborn comes in the first place from the urea cycle defects. The condition is usually observed in premature babies on ventilatory support during the first 24 hours after birth. Patients are usually boys, but also heterozygous girls. Characteristic is the lack of deep tendon reflexes, decreased pain sensitivity and development of hyperammonemic coma. The serum orotic acid levels are crucial for exact diagnosis.

The maple syrup urine disease is caused by deficiency of 2-ketodehydrogenase, which catalyzes the metabolism of leucine, isoleucine and valine. It is manifested through smell of urine, poor feeding, lethargy, encephalopathy, seizures. (Zinn AB, 2015)

The defects in the amino acids metabolism are another major group of inborn errors of metabolism. Most frequent in the neonatal period are lactic acidosis, methylmalonic, propionic and isovalerianic acidaemia.

In methylmalonic acidaemia, the baby is usually fine at birth, but then gradually come forward feeding problems, vomiting, lethargy and seizures. Attacks of severe repeated metabolic acidosis are observed and are triggered by a protein rich diet and infections. Muscular hypotonia, triangular mouth, high forehead are accompanied signs. (Burton BK, 2016, Matthews A, Robin N, 2016)

A deficiency of propionyl-CoA carboxylase is a specific feature of propionic acidaemia. Loss of appetite, vomiting, dehydration, hypotension, lethargy and convulsions, periodic episodes of metabolic acidosis are noted. Ketonaemia, neutropenia, thrombocytopenia and hypoglycemia are characteristic laboratory symptoms. Reduced enzyme activity in leukocytes proves diagnosis.

Typical for isovalerianic acidaemia is selective deficiency of the enzyme isovaleryl-CoA dehydrogenase. The acute form of disease presents by catastrophic clinic. The late onset one presents by periodic episodes of metabolic decompensation. Babies usually fall into coma. Laboratory findings point out secondary hyperammonemia, pancytopenia, ketoacidosis and hypocalcaemia. Diagnostic feature is the increased level of isovalerianic acid in the urine. (Matthews A, Robin N, 2016; Brunetti-Pieri N et al, 2016; Lorenz MJ, 2015)

Congenital lactate acidosis is characterized by a defect of the enzyme pyruvate dehydrogenase, pyruvate carboxylase and mitochondrial defects of electron transport chains. The early manifestation is severe acidosis or expressed neurological deficit without acidosis. (Chung WK, 2008)

Galactosemia, Von Gierke's disease (abnormal accumulation of glycogen) and hereditary fructose intolerance are referred to the defects of carbohydrates metabolism. Galactosemia in the neonatal period manifests after galactose intake. Early symptoms are jaundice, lethargy, vomiting, cataracts and bleeding. Typical symptoms are hyperbilirubinemia, liver dysfunction (coagulopathy, hypoglycemia, hypoalbuminemia and ascites), encephalopathy with cerebral edema,

metabolic acidosis, hypophosphataemia, hyperchloraemia, renal dysfunction and E. coli sepsis. Measure the activity of galactose-1-phosphaturidiltransferase in erythrocytes is the tool of first choice for right diagnosis.

Abnormal accumulation of glycogen (Von Gierke's disease) is a rare disease in the neonatal period. Clinically it is manifested by hypoglycemia, which is usually severe and can be accompanied by lactate acidosis, enlargement and dysfunction of the liver that develops 1-2 weeks later. It is diagnosed by liver biopsy, enzyme analysis and DNA diagnostic tests. (Burton BK, 2016; Matthews A, Robin N, 2016; Brunetti-Pierri N et al, 2016)

Hereditary fructose intolerance is characterized by deficiency of the enzyme fructose-1,6-biphosphataldolase. Symptoms occur after fructose or sucrose intake after feeding the child with fruit juices. Clinically are detected pallor, lethargy, poor feeding, vomiting, diarrhea, and hepatomegaly. Laboratory findings reveal hypoglycemia, hypophosphatemia, and elevated liver transaminases.

Reduced emission of hydrogen ions in the kidneys is the next possible reason for the development of metabolic acidosis. Disturbed acid-base balance may be due to the development of renal tubular acidosis. Disturbance in the proximal tubule leads to limited ability to emit hydrogen ions and incomplete reabsorption of bicarbonates, urine pH is below 5.5. Impaired excretion of hydrogen ions in the distal tubule segment causes the emission of large amounts of bicarbonate and urine pH is above 5.8. The diagnosis is based on metabolic acidosis and urine pH measurement. Biochemical studies show hypokalemia, hypochloraemia and glycosuria. (Seri I, 2008)

Late acidosis in premature infants occurs in healthy preterm infants at the age of 1 to 3 weeks and is characterized by mild to moderate acidosis and delayed growth. Acid excretion is increased due to excessive protein contain, leading to excessive synthesis of endogenous acids exceeding urinary capacity of immature kidneys. It is limited by the loss of bicarbonate and

reduced phosphate excretion. This is often self-limiting disease which is affected by renal maturation. (Seri I, 2008)

A specific cause of metabolic acidosis is the increased loss of bicarbonate in diseases of the gastrointestinal tract. Malabsorption often develops in children with short gut syndrome as a result of surgery. The most common causes of the syndrome are bowel resection after necrotizing enterocolitis, volvulus, and congenital anomalies as atresia of the jejunum and ileum and gastroschisis. Intestines after this operation lose part of the ileum and ileocecal valve. (Chen MK, 2012) The diagnosis is usually based on the need for continuous parenteral nutrition for more than 6 weeks.

Starvation is another possible cause of the condition. It may be a result of quantitative and qualitative malnutrition associated with a deficiency of energy and the consumption of fats and proteins or impaired assimilation of ingested food.

4. Conclusion

During the patient stay in the ward, we consistently excluded the most of possible reasons that lead to repeated episodes of metabolic acidosis. From all of the already mentioned forms of metabolic acidosis according to anionic difference, the metabolic diseases are characterized by increased anion gap > 16 mEq / L, and in our case the acidosis is with a normal anion gap. Blood sample is taken and sent to the National Genetic Laboratory in Sofia where diagnosis "metabolic disease" was rejected.

Finally, the short bowel syndrome was accepted as the most appropriate diagnosis. The recurrent metabolic acidosis was interpreted as a result of malabsorbtion, loss of bicarbonates, water and electrolytes. Intravenous infusion of bicarbonates leads to transient therapeutic effect. Therefore parenteral intake was replaced by oral one of optimal dose bicarbonates. Thus the acid-alkaline homeostasis was permanently restored.

Even though metabolic acidosis is often seen in the neonatal period, this case is an example that it can be part of rare diseases and syndromes. The lack of adequate therapy can lead to life-threatening arrhythmias, myocardial depression, respiratory muscle fatigue, seizures, shock and multiorgan failure.

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How to cite this article:

Elitsa Valerieva, Preslava Gatseva and Victoria Atanasova. (2017). Recurrent severe metabolic acidosis in prematurely born infant – Case Report. Int. J. Curr. Res. Med. Sci. 3(1): 15-20.

DOI: <http://dx.doi.org/10.22192/ijcrms.2017.03.01.003>