METHYLMALONIC ACIDEMIA IN CHILDREN – CASE PRESENTATION

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Abstract

We present the case of a one year and six months male infant, admitted to our Clinic in October 2014, for vomiting and hypotony. He is the fourth born child, full term, with a birth weight of 3080 g, naturally fed for 5 months, followed by an incorrectly diversified feeding, weaned at one year, with a normal psychomotor development, without significant AHC until the age of one year and 2 months. From the age of 1 year and two months, he was repeatedly admitted to hospital for vomiting associated with hypotony, dehydration syndrome up to coma, in September 2014, when he was admitted to ICU, the salt wasting syndrome being infirmed. At admission, he had no fever, was pale, with an altered general state, dark circles around his eyes, dry lips, lazy abdominal skin fold, hypotonic, lethargic, cardio-respiratory balanced, supple abdomen, without meningeal symptoms, his weight being 9000 g. We noticed that, every time he was admitted, the general state suddenly worsened the moment he started to vomit. The alkaline deposit, at admission, was 12 mEq/l and we corrected it after the administration of sodium bicarbonate i.v., p.o., maintaining it between 18 and 22 mEq/l – following this treatment the general state got stable with no more vomiting. We performed a series of biochemical seric and urinary tests, imagistic investigations, and an ophthalmologic examination and we considered that the vomiting occurred in the context of an organic acidemia. The infant was transferred to the Medical Genetic Department of the Hospital for Children in Cluj-Napoca, where specific tests were performed: the chromatography of the urinary organic acids pointed out a highly increased level of the methylmalonic acid and a moderate level of the uracil, results which suggested a methylmalonic acidemia. The patient remained in our clinic's records, being given a daily treatment with L-carnitine, Biocebral, dietetic regime, with a fair evolution.

Key words: methylmalonic acidemia, child

Introduction

The organic acidemias represent rare genetic diseases, characterized by the accumulation within the body of some organic acids which usually come from amino-acids or fat acids. The methylmalonic acidemia (described in 1967) is second only to the deficit of methylmalonyl-CoA mutase, necessary to transform the malonic acid into succinic acid. The enzyme requires, as a co-enzyme, adenosylcobalamine, a metabolite of vitamin B12. The gene of the enzyme is on the chromosome 6p; the enzyme deficiency (caused by 20 known mutations) can remain completely or partially unexpressed [1]. The disease is caused by the deficit of the specific mutase in approximately 50% of the patients and by the deficit of the co-enzyme (deficit or metabolism dysfunctions of vitamin B12) in the remaining 50%, the therapeutic answer to vitamin B12 being absent or present, respectively, in the two categories of patients [2].

Case presentation

Male-infant, aged 1year and 6 months, from rural area, was admitted to the 2nd Pediatric Clinic, Emergency County Hospital Craiova, in November 2014 (medical record 54657), for vomiting and hypotony.

Heredo-collateral antecedents: mother 32 years old - hypertiroidism, a healthy father - 38 years old, and 3 healthy brothers (16, 14, 7 years old).

Personal physiologic antecedents: 4th child, on term, normal birth with no sufferance, weight at birth 3010 g, 1 week physiologic jaundice, naturally fed for 4 months, incorrectly diversified at 5 months, weaned at one year, and fed with adult's food.

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He was treated against rickets with vitamin D3, and vaccinated according to the Health Ministry scheme. The psychomotor development was according to age stages.

Pathologic personal antecedents: repeated episodes of vomiting with hypotony and alteration of the general state in the last 4 months which required hospitalization. From 21.09 to 06.10.2014, the patient was admitted to ICU Clinic for incoercible vomiting followed by coma associated with hydro-electrolytic and acido-basic dysfunctions. We performed further investigations which revealed the absence of the salt wasting syndrome.

At admission: normal height for his age (79 cm), with a moderate deficit in weight (Weight= 9 Kg, PI= 0.79, NI= 0.85), no fever, an altered general state, pale, a discrete craniofacial dysmorphism, dark circles around his eyes, dry lips, lazy abdominal skin folds, bottom flared thorax, normal stetacustic pulmonary, rhythmic heart beats, HB= 112 b/min., supple abdomen, normal stool, hypotonic, lethargic, without meningeal symptoms.

Because the child was admitted once again with vomiting and a rapid alteration of his general state, presenting many episodes of the same symptomatology in the last four months (it started when the child was one year and six months old), and taking into account that his latest admission was to the ICU, in a coma, we decided that it was necessary to investigate him thoroughly in order to find the source of the vomiting.

Admission investigations: Hemogram: Hb= 8.8g%, Ht= 28%, HEM= 26pg, CHEM= 30g/dl, VEM= 87μ^3, L=6200/mm^3, NS= 30%, Ly= 61%, M=9%, Tr.= 323000/mm^3, VSH= 8/20 mm, urea= 15 mg%, creatinine= 0.36 mg%, GOT= 27 U/l, GPT= 18 U/l, cholesterol= 110 mg%, lipemia= 450 mg%, triglyceride= 112 mg%, total protein= 7.9 g%, total seric calcium= 8.4 mg%, ionic calcium= 3.85 mg%, sideremy= 21 μg/dl, ammoniac= 45.5 μmol/l (N=16-60), seric ionogram: Na= 129 mEq/l, K= 4.3 mEq/l, alkaline deposit= 12 mEq/l, glycemia= 64 mg, urine test: ketone bodies ++++, negative uroculture, normal ophthalmologic examination normal, normal abdominal ultrasound exam, eso-gastroduodenal transit – no modifications.

We excluded the possibility of urinary infections (negative urine culture), intracranial hypertension (normal ophthalmologic examination), malformations of the digestive tract (normal eso-gastroduodenal barium transit and abdominal ultrasound), and illnesses which could lead to recurrent vomiting.

The analyses we performed when admitted showed low values of hemoglobin and sideremy, the parameters of the lipidic metabolism, normal hepatic and renal functional tests.

At admission, we noticed very low values of the alkaline deposit (12 mEq/l), glycemia (64 mg%) and natremia (129 mEq/l) and the presence of ketone bodies in urine, things which made us monitor the values of the alkaline deposits, glycemia, seric and urinary ionogram, urinary and ketone body pH (table 1).

Table 1. Paraclinic Investigations in progress.

Parameters	*Date*										
	26.10	*30.10*	*31.10*	*1.11*	*2.11*	*3.11*	*4.11*	*5.11*	*6.11*	*13.11*	*16.11*
Alkaline Deposit (mEq/l)	12	14	21	14	15	20	18	19	23	31	22
Sanguine ionogram											
Na (mEq/l)	129	133	136	136	135	141	129	131	139	241	136
K (mEq/l)	4.3	3.7	3.8	4.3	4.3	3.2	4.4	3.9	3.7	4.6	3.7
Cl (mEq/l)	112	111	135	103	104	108	103	103	109	107	107
Glycemia (mg%)	64		67	88	67	83	64	67	86	65	70
Urinary Ph	5.5		3.5	5.5	6	6.5	6.5	6	6.5	8	7
Ketone bodies	++++	abs.	+	+++	abs	abs	abs	++	abs	abs	abs
Urinary ionogram											
Na (mEq/l)	116		253	116	179	208	208	231	146	152	171
K (mEq/l)	12.9		36	27.6	12.9	21	21.9	56.1	7.6	6.5	6.9
Cl (mEq/l)	63		130	105	6,3	170	167	156	136	125	104
Urinary ionogram – normal values *Na = 40-220 mEq/l* *K = 25-125 mEq/l* *Cl = 110-259 mEq/l*											

The patient received, as an emergency treatment, perfusion with physiological serum, then sodium bicarbonate, glucoses, and electrolytes, Quamatel i.v., eventually resulting in an improvement of the general state.

After returning to normal feeding, the child had a fair general state, but after several days, he presented nausea, then vomiting which was rapidly followed by hypotony and somnolence. Once the vomiting onset, we proceeded to emergency analyses which proved low levels of the alkaline deposits. Thus, we noticed that the cause of vomiting was the metabolic acidosis.

The repeated episodes of vomiting with hypertonia, the alteration of the general state associated with the onset of acute severe dehydration up to coma, hypoglycemia and metabolic acidosis were suggestive for an organic acidemia.

We contacted the Emergency Hospital for Children in Cluj-Napoca, the Medical Genetic Department, and following their recommendations the child received, daily, a solution of sodium bicarbonate p.o.; the vomiting episodes ceased and the general state was fair. The alkaline deposit was within normal limits.

Subsequently, the patient was transferred to the Medical Genetic Department of the Emergency Hospital for Children in Cluj-Napoca, where several specific tests were performed:

- The chromatography of the urinary organic acids which pointed out a significantly increased level of the methylmalonic acid (779 mmol/mol created, N< 20), and a moderately increased level of the uracil (99 mmol/mol created, N< 55)
- The chromatography of the plasmatic amino-acids did not highlight a deficit of the essential aminoacids, but it pointed out moderately increased values of glycine (475 μmol/l), glutamic acid (418 μmol/l), serine (228 μmol/l) and taurine (317μmol/l).

These results suggested a methylmalonic acidemia; a precise diagnosis can be set by determining the activity of the deficitary enzyme (methylmalonyl-CoA epimerase) at the level of fibroblasts and by identifying the mutation.

The patient remained in our clinic's records with the diagnosis:

- Methylmalonic acidemia
- 1st degree dystrophy
- Ferriprive anemia

The child received a hypoproteic diet (1-1.5g/kg/day), rich in carbohydrates, with regular meals, and avoiding the prolonged fasting.

He received a daily treatment with L-carnitine p.o. and Biocebral p.o., after quitting the alkalization treatment with sodium bicarbonate solution.

We determined the seric level of vitamin B12, which was within normal limits, fact that did not require the introduction of B12 within the treatment.

After discharge, he received Haussman Iron for the ferriprive anemia.

Discussions

The methylmalonic acidurias (MMA) are metabolic disorders resulting from deficient methylmalonyl-CoA mutase activity, a vitamin B_{12}-dependent enzyme. Genetic defects in the methylmalonyl-CoA mutase (MCM) gene result in methylmalonic acidemia which is inherited as an autosomal recessive disease [2].

This disorder can display a wide spectrum of clinical manifestations, spanning the prenatal period through late adulthood [3,4]. The incidence of methylmalonic acidurias ranges from 1:115,000 in Italy, to 1:169,000 in Germany, but remains unclear in China. However, its incidence appears to be higher than previous estimates when making a diagnosis of suspected cases using newborn screening studies or gas chromatography-mass spectrometry [3,5]. The pathophysiology of the complications observed in MMA patients is still not fully understood, although acute or chronic neurological signs may be caused by the accumulation of toxic compounds proximal to the metabolic block, including increased homocysteine concentrations and impaired methyl group metabolism, oxidative stress, and dysfunctional mitochondrial/ caspase pathway [3,6].

Methylmalonic acidemias are a group of inherited diseases characterized by lethargy, vomiting, developmental delays, hypotony, and enlargement of the liver. They involve defects in one of several proteins and enzymes that break down certain amino acids, fatty acids, and cholesterol in the body. Symptoms are due to the toxic build-up of these substances and their metabolites in organs and tissues [7].

Methylmalonic acidemia is a disease that varies in age of onset, severity, and responsiveness to vitamin B_{12} treatment. The most severe form of the disease is the most common, has onset in early infancy, and is least responsive to vitamin B_{12} treatment. Symptoms may include: vomiting, hypotony, lethargy, failure to thrive, hepatomegaly, hypothermia, coma or death, even with aggressive intervention [7]. Some individuals have onset in early childhood or later, and symptoms are often triggered by fasting, illness, or eating large amounts of protein. Symptoms are similar to the severe form; however, these individuals are typically more responsive to vitamin B_{12} treatment [8].

There is no cure for methylmalonic acidemia. Treatment typically includes a low protein diet, nutrition supplements, and vitamin B_{12}. Despite treatment, as many as 50% of individuals diagnosed in infancy die in early childhood. Methylmalonic acidemia is included on all newborn screening panels in the United States [9].

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