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A RARE CASE OF HIGH ANION GAP METABOLIC ACIDOSIS

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Methylmalonic aciduria is an inborn error in the organic acids metabolism. Deficiency of methylmalonyl CoA mutase or its coenzyme, adenosylcobalamine, leads to accumulation of methymalonic acid in body fluids. The disease manifests with recurrent episodes of dehydration, metabolic acidosis, coma and death. We report a case of methylmalonic aciduria diagnosed in a female infant who presented with recurrent episodes of high anion gap metabolic acidosis. The particularity of this case is the presence of a rare pathogenic mutation- homozygous c.556C>T (p.Arg186Trp). This is a form of vitamin B12-responsive methylmalonic aciduria. The frequency of this mutation is reported to be 0.0002 in european and american population, and it was not detected in afro-american population. Our patient receives treatment with vitamin B 12, levocarnitine and low protein diet and the outcome was good.

Keywords: metabolic acidosis, methylmalonic acidemia

INTRODUCTION

High anion gap metabolic acidosis is caused generally by the body producing too much acid or not producing enough bicarbonate. Organic acidemias, also called organic acidurias, are a group of metabolic disorders which disrupt normal amino acid metabolism, particularly branched-chain amino acids, causing a buildup of acids in body fluids.

Methylmalonic acidurias represent a group of heterogenous diseases caracterised by a defect in the metabolism of some aminoacids like isoleucine, methionine, threonine, valine and odd chain fatty acids, defect that leads to accumulation of methylamlonic acid in body fluids[1].

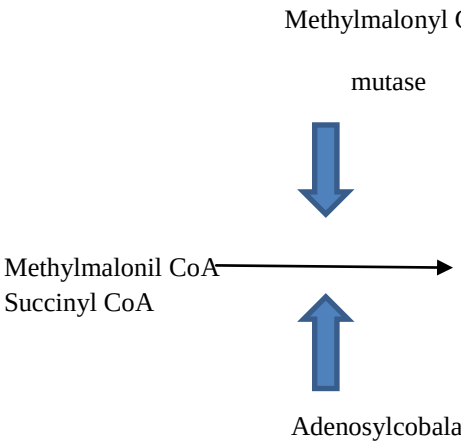

Figure 1 Methylmalonyl CoA mutase, the site of the defect in methylmalonic aciduria (adapted after [1])

The metabolic blockage is in most of the cases the deficient enzyme methylmalonil CoA mutase, which catalises the transformation of methylmalonil-CoA to succynil-CoA. In rare cases the metabolic blockage is found at the level of 5'-deoxyadenosylcobalamine, a vitamin B12-derived cofactor for methylmalonil-CoA mutase[2].

This explains why only some patients respond to treatment with high doses of vitamin B_{12}. In both cases the metabolic blockage results in accumulation of methylmalonic acid and its precursors[3].

The disease usually becomes manifest in infancy with recurrent episodes of vomiting, lethargy, dehydration, metabolic acidosis, high anion gap, ketonuria and in the absence of treatment can lead to coma and death. Undiagnosed patients could recover after vigorously treatment with parenteral fluids and electrolytes. High protein meals, infection or other kinds of catabolic stress could trigger another acute episode.

Laboratory findings, beside severe metabolic acidosis, include hypoglycemia, hyperammoniemia, hyperglycemia and masive ketosis. Particular facial features have been described, including high forehead, broad nasal bridge, epicanthal folds, a long smooth filtrum and a triangular mouth[1]. Other clinical signs include scalded skin, desquamation, and chronic periorificial dermatitis. This condition may be due to enzyme deficiency or multi-nutrient deficiency because of nutritional restriction[4].

CASE STUDY

We describe a female patient aged 1 year and 2 months old, with developmental delay, who came to the Emergency room in critical state, with Glasgow Coma Scale score of 4. The acute episode started a few days before admission with a respiratory intercurrent illness. It rapidly progressed to respiratory failure. From her personal history we note that she was born at 44 weeks of gestation, with normal birth weight- 3700g and Apgar score of 8. She had delayed developmental milestones and had no acute illness until admission.

She had particular facial features, including high forehead, broad nasal bridge, epicanthal folds, a long smooth filtrum and a triangular mouth (Figure 2 and 3).

Laboratory studies showed severe metabolic acidosis- pH was 7.03, high anion gap- 28.2, with normal glycemic levels and normal blood lactate. She was admitted to the Intensive Care Unit where she needed respiratory support for several days. Evolution was marked by recurrent episodes of metabolic acidosis with poor response to treatment. Intoxication was ruled out from anamnesis and she had no sign of kidney disease. A metabolic disorder was taken into consideration.

We tested for plasma and urinary amino acids, acylcarnitine profile, urinary organic acids, lactate and pyruvate in cerebrospinal fluid. We found elevated levels of methylmalonic acid in urine and elevated levels of propyonilcarnitine in blood and urine. Glycine levels were normal in plasma and urine. Suspicion of methylmalonic aciduria was raised and the patient was started on a low protein diet and high dose of vitamin B_{12} supplementation.

Figure 2 The patient aged 1 year and 7 months old

A few days after vitamin B_{12} treatment was started the patient was weaned off respiratory support, and 2 weeks after the treatment was started the patient was discharged.

After one month of treatment she received normal diet and continued with oral supplementation of vitamin B_{12}.

Two months later she came to the Emergency Room in critical state, with severe metabolic acidosis, with plasma pH of 6,94, high anion gap-36, masive ketosis and hypoglycemia. The episode was sudden, without an intercurrent illness or catabolic stress that could be incriminated as a trigger. The protein restrictive diet was started again after that, and the outcome was good.

The particularity of this case is the rare pathogenic variant mutation- homozygous c.556C>T (p.Arg186Trp)- this is a form of vitamin B_{12} responsive methylmalonic aciduria. The frequency of this mutation was raported to be 0.0002 in european and american population, and it was not described in afro-american population.

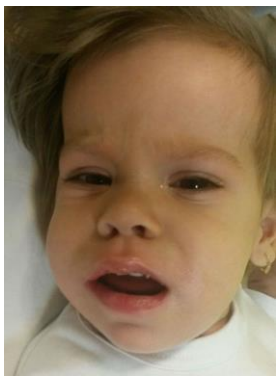

Figure 3 The patient aged 1 year and 7 months old

DISCUSSIONS

In every patient with high anion gap metabolic acidosis suspicion of organic acidemia should be raised. Our patient presented with recurrent episodes of high anion gap metabolic acidosis with poor response to treatment.

The clinical manifestation of the disease is acute and often associated with a respiratory or digestive intercurrent illness. Our patient presented with respiratory illness and the metabolic decompensation rapidly worsened her clinical state.

In vitamin B12 responsive methylmalonic acidemia treatment with high doses of vitamin B12 could not be enough. Our patient was stable when receiving a low protein diet, but when returning to normal diet she had an acute episode of severe metabolic acidosis. Her plasma vitamin B12 levels were high at the time and there was no catabolic trigger, such as an infection.

Mutation analysis showed a rare form of vitamin B12 responsive methylmalonic aciduria. After receiving treatment with high doses of vitamin B12 her neurologic outcome was good.

Establishing a firm diagnosis by mutation analysis helped providing an accurate treatment and prognostic orientation.

CONCLUSIONS

In every patient presenting with unexplained high anion gap metabolic acidosis, suspicion of organic acidemia should be raised. The dietary treatment of patiens with vitamin B_{12}-responsive methylmalonic aciduria should be closely monitored for protein intake.

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