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Propionic Acidemia with Neonatal Presentation: A Case with Fatal Outcome

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Abstract

Propionic acidemia is an autosomal recessive disorder of branched-chain amino acid metabolism, manifested by episodes of metabolic acidosis, hyperammonemia, and encephalopathy. This article reports the case of a female newborn with propionic acidemia presenting an unusually severe neonatal phenotype. This newborn, born to consanguineous parents, developed massive hyperammonemia without initial metabolic acidosis, leading to rapid neurological deterioration. Despite intensive treatment including hemodiafiltration, the infant died on day 32, highlighting the severity of the disease and the need for early diagnosis and genetic counseling.

Keywords

Propionic Acidemia, Hyperammonemia, Newborn, Metabolic Decompensation, Encephalopathy

1. Introduction

Propionic acidemia is an autosomal recessive inborn error of metabolism caused by a deficiency in propionyl-CoA carboxylase (PCC). It results from a mutation in the PCCA (Xsome 13) or PCCB (Xsome 3) genes involved in the catabolism of branched-chain amino acids, odd-numbered fatty acids, cholesterol side chains, thymine, and uracil [1] [2]. The incidence of the disease is very low, 1/150,000 in Western countries. The acute neonatal form manifests as unexplained or recurrent neurological distress from the first days of life with a symptom-free interval, which may be associated with digestive and hepatic signs (recurrent vomiting), often progressing to neurological deterioration that can lead to coma and a risk of death within a few days. Treatment includes extrarenal purification in cases of severe hyperammonemia, limiting the accumulation of toxic compounds through

a strict low-protein diet combined with sufficient carbohydrate and fat intake, and carnitine supplementation. The prognosis is often severe, with high mortality in early forms [3].

We report a case of neonatal propionic acidemia diagnosed at the Lille University Hospital in a newborn girl in her third week of life, who died despite metabolic management in accordance with current recommendations.

2. Observation

This is a newborn female, the seventh child of a couple who are first cousins. She was born at term by vaginal delivery without instruments, adapting well to extrauterine life, with no antenatal or postnatal abnormalities. An older sister has epileptic encephalopathy linked to a mutation in the CEP290 gene, but the current picture is different. Her stay in the maternity ward was uneventful. She was fed a mixed diet. She was discharged after two days. On day 19 of life, she was hospitalized for poor weight gain and axial hypotonia. The neurological examination revealed major axial hypotonia, poor motor skills, difficult eye tracking, lively osteotendinous reflexes, and rhythmic movements of the eyelids and limbs. She had lost 12% of her birth weight, with a blood glucose level of 0.76 g/L and acetonemia of 2.4 mmol/L. She was admitted to the intensive care unit for monitoring. She was transferred to the intensive care unit 24 hours later due to worsening neurological symptoms, increased hypotonia, and impaired consciousness. Initial laboratory tests showed blood glucose levels of 1.07 g/L and ketonemia of 1 mmol/L. Blood gases showed lactate levels of 1.5 mmol/L, mixed alkalosis with a pH of 7.53, pCO_2 of 26 mmHg, and bicarbonate levels of 13.9 mmol. Infectious disease tests were negative. The metabolic assessment showed hyperammonemia at 611 µmol/L (then 1078 µmol at 4 hours). Initial management included immediate fasting, high carbohydrate calorie intake (12 mg/kg/min) with calcium gluconate without protein or lipids. The condition was marked by a rapidly progressive worsening of hyperammonemia. Early purification treatment by hemodiafiltration allowed for temporary normalization of ammonia levels. The blood amino acid profile was normal (glutamine and citrulline), ruling out a urea cycle deficiency. Chromatographic analysis of urinary organic acids revealed increased excretion of 3-hydroxypropionic acid, 2-methyl citrate, propionylglycine, and tiglylglycine, confirming the diagnosis of propionic acidemia. Treatment consisted of an anabolic carbohydrate-lipid infusion. The resumption of enteral nutrition with Modilac Doucea 1st age milk s poorly tolerated, requiring parenteral nutrition with essential amino acids lacking leucine/valine/isoleucine. The course of the disease was marked by a new decompensation with a rise in ammonia levels requiring the resumption of hemodiafiltration, a picture of septic shock with major inflammatory syndrome (CRP 262 mg/L maximum, PCT 66 ng/ml), without bacteriological identification, and bone marrow aplasia. Cardiac ultrasound did not reveal cardiomyopathy. The initial EEG showed a discontinuous, disorganized trace, followed by the appearance of right hemispheric irritative abnormalities, which were more

pronounced during slow-wave sleep, with slow rhythmic discharges in the right frontal lobe. Brain MRI revealed bilateral lesions of the substantia nigra, basal ganglia, and amygdala.

Given the very poor prognosis due to the brain damage present and the progression of the disease despite optimal treatment, a collegial decision was made to shift the therapeutic approach toward palliative care. Death occurred on day 32 of life. Genetic testing for PCCA or PCCB mutations was performed on the patient and parents.

3. Discussion

Propionic acidemia (PA), an autosomal recessive disorder of amino acid and odd-chain fatty acid metabolism, was first described in 1961 and is characterized by elevated levels of glycine in plasma and urine. The biochemical defect involves the conversion of propionyl-CoA to methylmalonyl-CoA by the enzyme propionyl-CoA carboxylase (PCC). The accumulation in the body of metabolites upstream of the enzyme block (mainly propionic acid, methylmalonic acid, and their CoA derivatives, methylcitrate, 3-OH-propionate, propionylglycine, and propionylcarnitine) results in a picture of endogenous intoxication. Propionyl-CoA carboxylase is a complex and large mitochondrial enzyme which, when dysfunctional, generally causes a serious metabolic disorder with significant morbidity and mortality. The toxicity affects many organs (brain, liver, kidney, heart, skin, hematopoietic system) [4].

In the classic form with neonatal onset, as in our patient, symptoms appear within a few days to a few weeks when protein intake increases [5]-[7]. The clinical picture combines nonspecific digestive and hepatic signs, weight loss, neurological involvement with muscle hypotonia or hypertonia, irritability, lethargy progressing to coma, and seizures. However, these symptoms are not specific, which explains the delay in diagnosis and treatment. In propionic acidemia, hyperammonemia is generally moderate. Accumulation of propionyl-CoA metabolites (particularly propionyl-CoA itself and methylmalonyl-CoA) inhibit N-acetylglutamate synthase (NAGS), an enzyme essential for the activation of carbamoyl phosphate synthetase I (CPS I). This inhibition blocks the urea cycle, explaining the severe hyperammonemia that dominated the initial clinical picture in our patient, before the onset of significant metabolic acidosis, which occurred secondary to the progressive accumulation of organic acids.

The absence of initial acidosis in this case is unusual but has already been described in certain very early forms where ammoniogenesis dysregulation predominates. The diagnosis is based on urinary organic acid chromatography, which shows a characteristic profile with 3-hydroxypropionate, 2-methylcitrate, and propionylglycine. Carboxylase testing on fibroblasts or genetic analysis confirms the diagnosis.

In our observation, the patient presented with bone marrow failure, reflecting profound hematopoietic impairment. This severe pancytopenia could result from

toxic bone marrow suppression linked to the accumulation of organic metabolites (particularly propionyl-CoA and its derivatives), which are responsible for altering the mitochondrial function of hematopoietic stem cells. The literature reports that leukopenia is the most common hematological complication during propionic acidemia, but cases of thrombocytopenia, anemia, and even bone marrow failure have also been described [8]. Dilated and hypertrophic cardiomyopathy have also been described in the literature [9]. Early identification, evaluation, and treatment of metabolically unstable patients with PA are important for improving survival and reducing morbidity. In regions where expanded neonatal screening panels are available, patients with PA can be identified by elevated propionylcarnitine (C3). Consanguinity increases the risk of autosomal recessive disorders such as propionic acidemia, hence the importance of genetic counseling.

Treatment aims to reduce propionyl-CoA production, correct metabolic disorders, and prevent decompensation. Hemodialysis or hemodiafiltration is the treatment of choice for hyperammonemia > 500 µmol/L. Additional measures include glucose and lipid infusion to block catabolism. s carnitine and biotin supplementation, as well as the gradual reintroduction of a low-protein diet with formulas low in branched-chain amino acids [8]. The neurological damage observed on MRI is linked to the direct toxicity of metabolites on neurons, particularly the basal ganglia and substantia nigra, and their presence is a negative prognostic factor [10]. The decision to focus the treatment plan on comfort was based on the observation of irreversible brain damage and an unfavorable prognosis despite maximum treatment.

4. Conclusions

This case illustrates the severity of neonatal propionic acidemia and the importance of rapid diagnosis, aggressive metabolic management, and family genetic follow-up for prenatal counseling.

The dramatic progression underscores the need for expanded neonatal screening, already implemented in several countries, to enable early management before the first decompensation.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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