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Case Report

GESDAV

Rare case of an infant with glutathione synthetase deficiency

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ABSTRACT

An infant has generalized glutathione synthetase deficiency (GSD). Pyroglutamic aciduria (5-oxoprolinuria) is a rare autosomal recessive disorder caused by either GSD or 5-oxoprolinase Deficiency. The severe form of the disease, generalized GSD, is characterized by acute metabolic acidosis, usually present in the neonatal period with hemolytic anemia and progressive encephalopathy. We report a male infant who had a severe metabolic acidosis with high anion gap, hemolytic anemia, and hyperbilirubinemia. High level of pyruglutamic acids was detected in his urine. He passed away of severe metabolic acidosis and sepsis.

KEY WORDS: Glutathione synthetase deficiency, newborn

INTRODUCTION

Pyroglutamic aciduria (5-oxoprolinuria) is a rare autosomal recessive disorder caused by either glutathione synthetase deficiency (GSD) or 5-oxoprolinase deficiency. 5-oxoprolinase Deficient patients have normal acid-base status and do not have hemolytic anemia [1].

GSD has two clinical forms: Generalized and erythrocyte GSD. The former is severe with clinical features of severe metabolic acidosis, hemolytic anemia, hyperbilirubinemia, neurologic disabilities and sepsis [1,2].

It has been described in 40 patients from 35 families [2]. Excess 5-oxoproline (also known as pyroglutamic acid) production is a rare cause of high anion gap metabolic acidosis (HAGMA). It is an intermediary in the 8-glutamyl cycle, which facilitates the transport of the tripeptide glutathione (glutamyl-cystinyl-glycine) and its constituent amino acids across cellular membranes and regenerates glutathione intracellularly. Reduced glutathione is required for detoxification and minimization of source(s) of support: None. Free – radical-induced oxidative stress, as shown in Figure 1.

Here we report an infant with generalized GSD.

CASE REPORT

The male infant was admitted to our pediatric intensive care unit for severe failure to thrive and marasmus when he was 3 months old, born after a term pregnancy, by normal vaginal delivery to a healthy mother, G3P3A0. His parents were non-consanguineous. They had two healthy older siblings. Birth weight 4000 g. He was normal at birth and was fed mother's milk, at 1 week of life started to have repetitive episodes of vomiting after each feed, not projectile, not bilious and non-bloody, so regular infant formula was added to breast feeding. At 2 months 1 week of age (3 weeks prior to presentation) patient started to have diffuse scaly skin lesion associated with loose frequent stools and decrease in PO intake in addition to persistent vomiting. On physical examination upon presentation, weight 3560 g (below 5th percentile), height 53 cm (below 5th percentile), vital signs T = 37°C P = 146/min respiratory rate = 46/min, blood pressure = 90/50 mmHg, oxygen

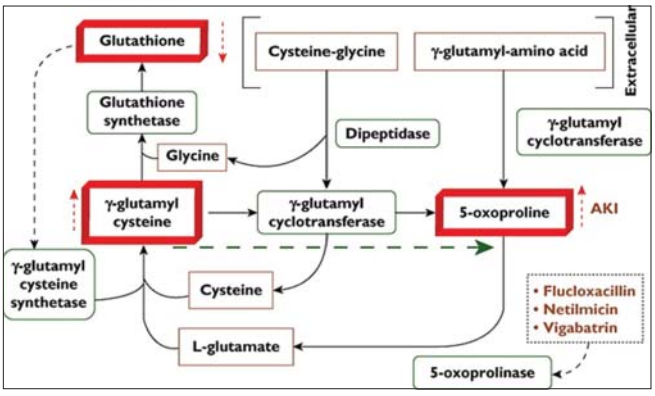

Figure 1: 8-glutamyl cycle showing generation of 5-oxoproline (pyroglutamic acid)

saturation = 99%. Patient was irritable, with diffuse erythematous skin with scaly lesions associated with dry mucus membrane, cracked lips, sunken eyes, and pitting edema of upper and lower extremities otherwise physical exam was unremarkable with no hepato-splenomegaly and normal heart sounds.

Initial investigations showed: Hemoglobin (Hb)= 10.1 g/dl, white blood cells = 15,000 (45% seg, 48% lymph), platelets = 480,000, blood urea nitrogen = 10 mg/dl, creatinine = 0.2 mg/dl, electrolytes: Sodium = 135 mmol/L, potassium = 3.5 mmol/L, chloride = 104 mmol/L, carbon dioxide = 19 mmol/L, albumin = 2.2 g/dl (N.V = 3, 5-5 g/dl), serum glutamic-pyruvic transaminase (SGPT) 55 U/L (N.V = 0-50 U/L), immunoglobulin E specific cow's milk (F2) was positive (Class 2), so patient put on extensively hydrolyzed formula. After 48 h, patient started to develop in addition fever, follow-up CBCD showed a drop in Hb to 8.1 g/dl that further decreased to 6.9 g/dl in the following 24 h, urine culture revealed *Klebsilella pneumoniae* >100,000 CFU/ml (extended-spectrum beta-lactamase) so started on cefepime, 24 h later his condition deteriorated and started to have increased tachypnea and restlessness with profuse diarrhea and pallor, CBCD showed further drop in Hb = 6.7 g/L, lactic dehydrogenase 985 U/L (N.V = 120-300 U/L), haptoglobin <6 mg/dl (N.V = 30-200 mg/dl), increase in liver function tests SGPT 811 U/L (N.V 0-50 U/L), serum glutamic oxaloacetic transaminase 1300 U/L (N.V = 0-50 U/L), bilirubin 17 mg/dl (direct bilirubin = 13 mg/dl), carbon dioxide 12 mmol/L, anion gap = 23 and patient started to have profound jaundice with massive hepatomegaly in addition to his bad situation. Patient had drop in Hb despite packed red blood cells transfusions.

Due to progressive tachypnea, restlessness and change in level of consciousness patient was intubated and attached to mechanical ventilation. Liver biopsy performed to reveal ballooning of hepatocytes with abundant clear cytoplasm consistent with steatohepatitis. Urine organic acids were positive for: Pyroglutamic acids, 4 hydroxyphenyl lactic acids, and 4 hydroxy phenyl puruvic Acids, which were consistent with diagnosis of pyruglutamic aciduria. Patient had refractory acidosis despite sodium bicarbonate infusion. Some of his parameters were shown in Table 1.

Table 1: Most important parameters as per hospitalization day

Parameters	Day 2	Day 3	Day 4	Day 7
ABG	pH=7.39	pH=7.33	pH=7.3	pH=7
	PCO_2=26	PCO_2=36	PCO_2=24	PCO_2=20
	HCO_3=16	HCO_3=18	HCO_3=12	HCO_3=10
CBC	Hbg=8.1	Hbg=6.9	Hbg=6.7	Hbg=5.9
	Hct=24	Hct=20	Hct=20	Hct=18
Bilirubin	T=7.4	T=7	T=11	T=17
	D=6	D=5.9	D=8.9	D=13
Plasma amino acids			Normal	
Urine organic acids			Pyroglutamic acids, 4 hydroxyphenyl lactic acids, 4 hydroxy phenyl puruvic acids	

Hb: Hemoglobin

DISCUSSION

Excess 5-oxoproline (also known as pyroglutamic acid) production is a rare cause of HAGMA. It is an intermediary in the gamma-glutamyl cycle, which facilitates the transport of the tripeptide glutathione (glutamyl-cystinyl-glycine) and its constituent amino acids across cellular membranes and regenerates glutathione intracellularly. Reduced glutathione is required for detoxification and minimization of free-radical-induced oxidative stress, excess of 5-Oxoproline is generated via the gamma-glutamyl cyclo-transferase enzyme when glutathione synthetase is deficient [1].

Glutathione depletion is seen in liver disease, paracetamol use, glycine deficiency, malnutrition and severe sepsis [2]. It is oxidized by the enzyme 5-oxoprolinase to L-glutamate; However, certain drugs (fucloxacillin, netilmicin and vigabatrin) can inhibit 5-oxoprolinase, hence preventing its degradation [3]. 5-Oxoproline concentrations are also increased in patients with burns and those on total parenteral nutrition [1]. A common thread among case reports of pyroglutamic acidosis is its association with critical illness and significant comorbidities, including sepsis and renal failure. The typical presentation occurs in a patient who develops an acutely altered level of consciousness and the clinical manifestations of metabolic acidosis during a prolonged hospital stay.

Clinically there are two different forms of GSD. The severe form of the disease, generalized GSD, is characterized by decreased cellular levels of glutathione, severe metabolic acidosis, massive urinary excretion of 5-oxoproline, elevated levels of 5-oxoproline in blood and cerebrospinal fluid, increased rate of hemolysis, central nervous system symptoms and granulocyte dysfunction. The milder form is associated with low levels of erythrocyte glutathione and compensated hemolytic disease and does not lead to 5-oxoprolinuria [4-7]. GSD is inherited as autosomal recessive trait.

Clinical signs usually first appear during the neonatal period. After the neonatal period, the condition is usually stabilized, but may deteriorate during an infection due to severe acidosis or electrolyte imbalance. Five of 40 patients reported in the literature died in the neonatal period due to severe acidosis and infection [4]. Increased susceptibility to bacterial infections due to defective granulocyte function was reported in two patients with GSD [8].

The generalized form is postulated to be due to mutations affecting the catalytic properties of the enzyme, whereas the erythrocyte form of GSD is postulated to be due to a mutation primarily affecting the stability of the enzyme [5].

Treatment involves correction of metabolic acidosis initially by parenteral compounds followed by oral maintenance, antibiotic treatment if there is an infection, and supportive care. In the neonatal period, it is important, especially to prevent hyperbilirubinemia in order to protect the brain from

kernicterus. Anemia often needs to be treated with blood transfusion. As there is increased sensitivity to oxidative stress, such anti-oxidative agents as vitamin E, C, and N-acetylcysteine have been used [9].

CONCLUSION

Pyroglutamic aciduria (5-Oxoprolinuria) should be considered in a newborn with severe metabolic acidosis, hemolytic anemia, hyperbilirubinemia and neurologic deterioration. Excessive urinary 5-oxoproline excretion must be investigated to confirm the clinical diagnosis. Prenatal diagnosis is available and should be offered to parents.

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