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Glutaric Aciduria type I and acute renal failure — Coincidence or causality?

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ABSTRACT

Glutaric Aciduria type I (GA-I) is a rare organic acidemia, caused by mutations in the *GCDH* gene, and characterized by encephalopathic crises with neurological sequelae. We report herein a patient with GA-I who presented with severe acute renal failure requiring dialysis, following an acute diarrheal illness. Histopathological evaluation demonstrated acute tubular necrosis, and molecular diagnosis revealed the patient to be homozygous for a previously unreported mutation, p.E64D. As renal impairment is not part of the clinical spectrum typical to GA-I, possible associations of renal failure and the underlying inborn error of metabolism are discussed, including recent advancements made in the understanding of the renal transport of glutaric acid and its derivatives during metabolic disturbance in GA-I.

1. Introduction

First described in 1975, Glutaric Aciduria type I (GA-I) is a rare autosomal recessive disease caused by deficiency of glutaryl-CoA-dehydrogenase (GCDH), and characterized by encephalopathic crises and subsequent irreversible neurological impairment. Over 200 disease-causing mutations have been described

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in the *GCDH* gene, located on chromosome 19p13.2. If diagnosed prior to neurological sequelae, GA-I is considered a treatable condition, and it is included in newborn screening programs in many countries [5].

1.1. Renal involvement in Glutaric Aciduria type I patients

A review of the literature surfaces several case reports associating GA-I and renal disease. In one such case, an 8.5 year old boy with GA-I was reported to develop rhabdomyolysis and acute renal failure following acute status dystonicus, subsequently necessitating two weeks of hemodialysis [2]. While the renal impairment was attributable to the rhabdomyolysis itself, it is important to note that the patient did undergo prolonged resuscitation efforts following cardiopulmonary arrest, which may also point to renal hypoxic injury as an additional mechanism of insult.

Another association between GA-I and renal disease, is the rare scenario in which the latter proves as the inciting event following which the underlying metabolic disorder is diagnosed. This was the case of a 3 month old patient reported to present with an early-onset of nephrotic syndrome leading to the metabolic derailment [4].

It is important to note that renal insufficiency may cause a false-positive result for GA-I in neonatal screening. In a study reviewing 173,846 newborns undergoing neonatal screening in a center in Germany over a period of four years, 53 were initially positive and 11 remained positive on recall testing, however none of these 11 infants were confirmed to have GA-I, whereas all had either congenital or acquired renal insufficiency [3].

2. Case presentation

A 6 year old boy, known to have GA-I, was transferred to our tertiary center for urgent dialysis treatment due to severe acute renal failure following a diarrheal illness and an initial suspicion of hemolytic uremic syndrome (HUS).

The patient had been initially diagnosed at our center at the age of 11 months. He was a second child to first-degree consanguineous parents of Arab–Muslim descent, born preterm at 28 weeks of gestation, with a birth weight of 1700 g. His development was reported to be normal until the age of ten months, at which a febrile illness accompanied by persistent diarrhea had led to metabolic acidosis, renal failure and multiple seizures. Based on high glutaric acid and 3-hydroxyglutaric acid levels in the urine, the diagnosis of GA-I was made, and a lysine-free low-tryptophan diet was initiated. Of note, brain atrophy was demonstrated on computed tomography.

At the age of 6 years, the patient was hospitalized at another center following a 10-day history of diarrhea without fever, and subsequent oliguria. Physical examination there had shown macrocephaly, psychomotor delay, pallor and periorbital edema, as well as crackles on lung auscultation. Abdominal ultrasound had revealed ascites, and laboratory evaluation was notable for thrombocytopenia (Platelets, 51 K/μl), anemia (Hemoglobin, 9.5 g/dl), severe renal failure (Creatinine, 8.6 mg/dl; Urea, 273 mg/dl), elevated liver transaminases (AST, 1043 IU/l; ALT, 778 IU/l) and elevated inflammation markers (C-reactive protein, 96 mg/l). Prior to transfer to our center, and under suspicion of HUS, he was treated with Ceftriaxone, Rivotril, Calcium Gluconate, L-Carnitine, Sodium Bicarbonate and intravenous fluids, and a suprapubic catheter was introduced due to difficulty placing a urinary catheter.

Upon admission to our pediatric intensive care unit, he was somnolent but responded to painful stimuli, with equal and responsive pupils and no meningeal signs, with mild respiratory distress, spasticity and scissor-like position of the lower limbs. Due to excessive blood pressures (160/100 mm Hg), Amlodipin treatment was initiated, and later switched to Labetalol. He was treated antibiotically with Ceftriaxone, and an extensive evaluation for infectious agents was positive for Acinetobacter in blood cultures, Enterobacter and Pseudomonas in peritoneal fluid cultures and Parainfluenza-3 in nasal swab, with negative throat, urine and stool cultures.

Laboratory tests upon admission revealed severe renal failure (Serum Creatinine, 9.1 mg/dl; Urea, 243 mg/dl), anemia (Hemoglobin, 9.3 g/dl), Ammonia of 63 μg/dl and elevated total CPK to 3646 IU/l. Urinalysis showed pH of 8.0, moderate hematuria and proteinuria, Urine Glucose of 28 mg/dl, with no leukocyturia or nitrates, and urine myoglobin was 63 μg/l. Upon admission, urine organic acid profile showed highly elevated glutaric acid and 3-hydroglutaric acid, as well as elevated lactic acid, ketone bodies and adipic