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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

acid. Renal ultrasound showed normal-sized kidneys with an echogenic cortex, no hydronephrosis or renal vein thrombosis, and moderate ascites. An antegrad cystography was performed *via* suprapubic catheter, and demonstrated normal filling and incomplete emptying of the bladder with an intact urethra. During his hospitalization, the patient required peritoneal dialysis for over a week, followed by significant laboratory and clinical improvement. After removal of the suprapubic catheter, he began giving urine adequately, and laboratory tests upon discharge showed a significant improvement of renal function, however not yet reaching normal limits (Creatinine, 1.29 mg/dl; Urea, 45 mg/dl). Due to bradicardia and changes in consciousness level, a brain CT was performed and had again shown brain atrophy.

In order to confirm the initial diagnosis of Glutaric Aciduria type I, DNA was extracted from peripheral blood, and sequencing of the *GCDH* gene was performed, and had revealed the patient to be homozygous for a previously undescribed mutation, p.E64D (c.192G > T; Human CCDS Transcript no. CCDS 12286), causing a substitution of Glutamic acid to Aspartic acid (Fig. 1A). PolyPhen analysis showed the mutation to be potentially damaging, with a score of 0.865 (Sensitivity: 0.83; Specificity: 0.93) (Fig. 1B), and multiple alignment analysis demonstrated position c.192 to be conserved throughout several species (Fig. 1C).

Finally, as the etiology for the renal failure was not fully understood, nor was it explained by his baseline inborn error of metabolism, a kidney biopsy was obtained on the sixth day of hospitalization (18 days after the onset of the acute intercurrent illness). The biopsy was negative for immune complexes on immunofluorescence studies, showed glomeruli of normal morphology, and significant tubular damage, with distended tubules, damaged epithelial cells, no brush border and cellular debris in the tubular lumen, with edema of the interstitium, on both light- and electron-microscopies (Fig. 2).

3. Discussion

The patient described herein presented with severe acute renal failure following an intercurrent illness, which in itself is not a common or known part of the clinical spectrum of his underlying inborn error of metabolism, GA-I. While the evaluation of the nature of his renal impairment brought to the diagnosis of acute tubular necrosis, the question remained — what was the underlying mechanism, and was it directly associated to the GA-I. Several explanations may be suggested.

First, it is important to note that recent research has shed new light on the renal transport of glutaric acid and its derivatives during metabolic disturbance in GA-I. Using micro-array analyses in a mouse model of GA-I, Mühlhausen and colleagues have shown that the sodium-dependent dicarboxylate cotransporter 3 (NaC3) was found to mediate the translocation of glutaric acid (GA) and 3-hydroxyglutaric acid (3OHGA), and the organic anion transporters (OAT) 1 and 4 to be transporters of GA, 3OHGA and of D-2- and L-2-hydroxyglutaric acid (D2OHGA, L2OHGA) in the cells of the proximal tubule in the kidney [7,8]. Furthermore, they have recently demonstrated that during induced metabolic crises in the mouse model, the OAT1 transporters undergo mislocalization to the apical membranes with thinning of the proximal tubule brush border membranes. In addition, evidence of functional tubulopathy was shown, underscoring the putative pathogenetic importance of renal proximal tubule alterations in metabolic derailment of the GA-I model [1]. With respect to these findings, one may speculate that indeed renal proximal tubulopathy may be part of the GA-I metabolic derailment, as seen in our patient.

Second, the renal insult may have been indirectly associated with GA-I, consequently bringing the patient to seek medical attention with renal failure as the presentation, as was the case in the aforementioned sporadic reports. For instance, acute renal failure might have followed rhabdomyolysis, metabolic acidosis or administration of drugs with tubular necrosis as an adverse event (although the therapeutic treatment preceding the severe renal failure in our patient did not include NSAID's or other drugs commonly associated with this complication).

Third, one may argue that the renal failure was a unique and uncommon phenotype associated with the previously unreported mutation found in our patient, p.E64D, although this is less likely, as is the possibility of sheer chance or circumstantial association.

In addition, the patient was initially treated under a working diagnosis of hemolytic–uremic syndrome (with anemia, thrombocytopenia and acute kidney injury as part of the acute presentation). As the pathogenesis of HUS is characterized by microangiopathy, it is also worth mentioning that 3-hydroxyglutaric acid has been previously shown to produce vascular dysfunction both *in vitro* and *in vivo*, including reduction of endothelial chemotaxis and disruption of structural vascular integrity [6], and thus one may argue that the

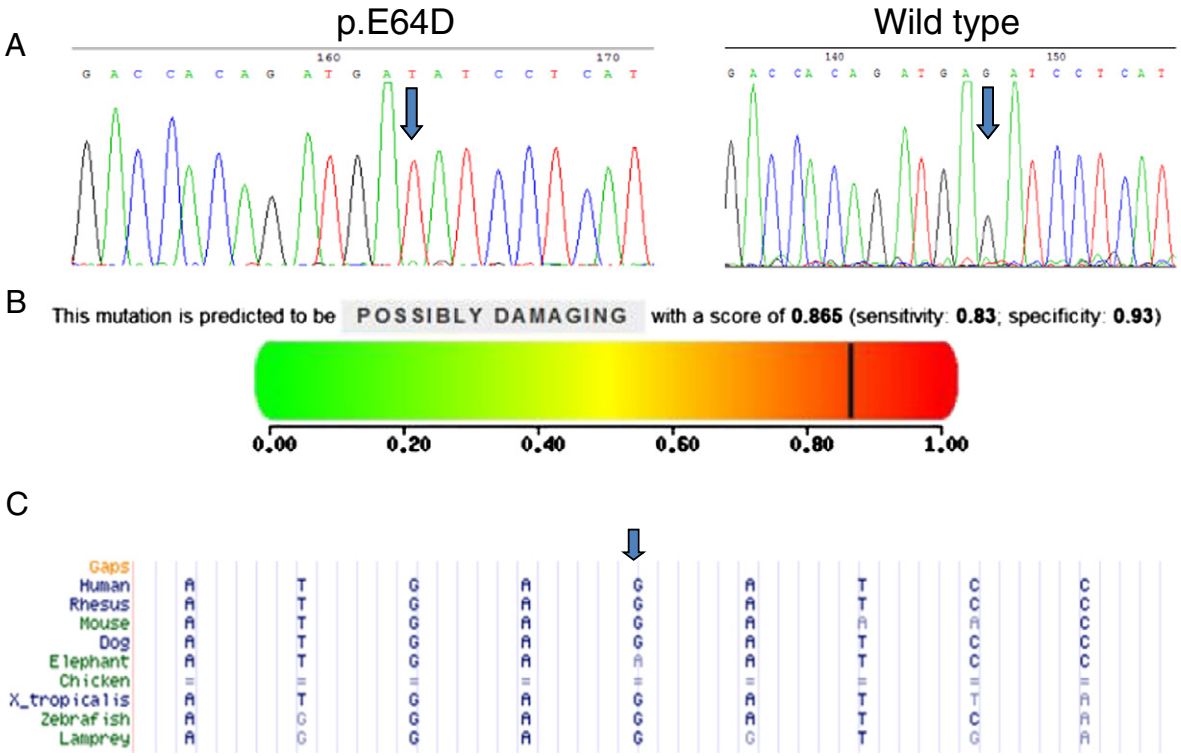

Fig. 1. Molecular evaluation of a GA-I patient presenting with severe renal failure. A) Chromatogram demonstrating a p.E64D previously unreported mutation in the *GCDH* gene, for which the patient was found to be homozygous. B) PolyPhen analysis of the same mutation. C) Multiple sequence alignments showing that c.192G is conserved throughout different species.

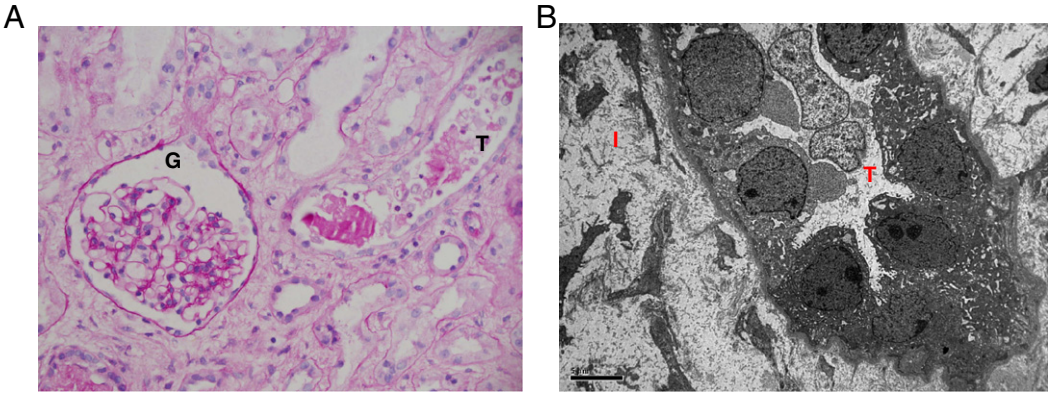

Fig. 2. Light (A) and electron (B) microscopy of kidney biopsy, revealing intact glomeruli (G), with edematous interstitium (I) and distended proximal tubules (T) with damaged epithelial cells, lack of basement membrane and cellular debris in the lumen, consistent with tubular necrosis.

acute metabolic derailment of GA-I and the subsequent elevation of the pathogenic metabolites might have played a role in the development of the HUS-like signs and symptoms.

In conclusion, while the severe renal impairment seen in our patient may have developed in several putative mechanisms, the case underscores the importance of early evaluation of renal function in any patient with GA-I who presents during an acute illness, as well as aggressive treatment of the underlying condition whenever possible.

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