Glutaric Aciduria Type 1 and Acute Renal Failure: Case Report and Suggested Pathomechanisms

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Received: 18 May 2017 / Revised: 14 June 2017 / Accepted: 22 June 2017 / Published online: 12 July 2017
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Abstract Glutaric aciduria type 1 (GA1) is caused by deficiency of the mitochondrial matrix enzyme glutaryl-CoA dehydrogenase (GCDH), leading to accumulation of glutaric acid (GA) and 3-hydroxyglutaric acid (3OHGA) in tissues and body fluids. During catabolic crises, GA1 patients are prone to the development of striatal necrosis and a subsequent irreversible movement disorder during a time window of vulnerability in early infancy. Thus, GA1 had been considered a pure “cerebral organic aciduria” in the past. Single case reports have indicated the occurrence of acute renal dysfunction in children affected by GA1. In addition, growing evidence arises that GA1 patients may develop chronic renal failure during adulthood independent of the previous occurrence of encephalopathic crises. The underlying mechanisms are yet unknown. Here we report on a 3-year-old GA1 patient who died following the development of acute renal failure most likely due to haemolytic uraemic syndrome associated with a pneumococcal infection. We hypothesise that known GA1 pathomechanisms, namely the endothelial dysfunction mediated by 3OHGA, as well as the transporter mechanisms for the urinary excretion of GA and 3OHGA, are involved in the development of glomerular and tubular dysfunction, respectively, and may contribute to a pre-disposition of GA1 patients to renal disease. We recommend careful differential monitoring of glomerular and tubular renal function in GA1 patients.

Abbreviations

3OHGA	3-Hydroxyglutaric acid
E-IMD	European registry and network for intoxication-type metabolic diseases
GA	Glutaric acid
GA1	Glutaric aciduria type 1
GCDH	Glutaryl-CoA dehydrogenase
GFR	Glomerular filtration rate
HUS	Haemolytic uraemic syndrome
LDH	Lactate dehydrogenase
OAD	Organic aciduria

Introduction

Glutaric aciduria type 1 (GA1, OMIM 231670) is caused by the autosomal-recessively inherited deficiency of glutaryl-CoA dehydrogenase (GCDH, E.C. 1.3.8.6), a mitochondrial matrix enzyme involved in the degradation of lysine and tryptophan. Affected patients accumulate the pathologic metabolites glutaric acid (GA) and 3-hydroxyglutaric acid (3OHGA) and glutaryl-CoA, and are prone to encephalopathic crises during a time window of vulnerability up to 72 months of age, with subsequent irreversible movement disorder due to injury of striatal neurons (Goodman and Frerman 2001). Early diagnosis of the disease by newborn screening is essential to avoid irreversible neurological sequelae. Treatment includes pre-symptomatic implementation of a lysine-restricted diet, carnitine supplementation, and a sufficient emergency management to avoid catabolism (Boy et al. 2017). The impairment of mitochondrial energy production reported in various in vitro and in vivo models appears to play a role in

Communicated by: Georg Hoffmann

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the pathophysiology of GA1, although the pathomechanisms leading to neurodegeneration are not yet fully understood (Jafari et al. 2011; Lamp et al. 2011). Animal and cellular models have demonstrated that the blood–brain barrier shows only very limited permeability for GA and 3OHGA. Thus, when produced intracerebrally, these metabolites accumulate in the brain compartment (Keyser et al. 2008; Sauer et al. 2006). GA and 3OHGA are excreted into urine via active tubular transport processes (Mühlhausen et al. 2008).

The haemolytic uraemic syndrome (HUS) belongs to the thrombotic microangiopathies. It commonly occurs in children and presents primarily with renal failure, haemolytic anaemia and thrombocytopenia. The most abundant trigger is the Shiga toxin of enterohaemorrhagic *E. coli*. But also other causes, e.g. inborn deficiencies in the complement system, or invasive *Streptococcus pneumoniae* infections, have been reported (Noris et al. 2012).

Here, we report on a 3-year-old girl with GA1 who died from renal failure most likely caused by pneumococcus-associated HUS. We hypothesise that GA1 may have been a predisposing factor for the acute renal failure that complicated this patient's pneumococcal sepsis, in that GA1 may promote increased endothelial vulnerability and thus the development of HUS.

Case Presentation

The girl was the first child of healthy, consanguineous parents of Turkish descent. GA1 was diagnosed by newborn screening. Subsequently, analysis of organic acids in urine detected a “high excretor” status (GA 2,650 mmol/mol creatinine; 3OHGA 92 mmol/mol creatinine; Baric et al. 1999). Genetic analysis revealed the homozygous pathogenic variant p.Arg402Trp in the *GCDH* gene, and residual GCDH enzyme activity in fibroblasts was found to be absent. A lysine-restricted diet, carnitine supplementation and adequate emergency management were implemented according to current therapy guidelines (Boy et al. 2017). Until the age of 3 years, the clinical course was uneventful with normal psychomotor development, absence of encephalopathic crises and lack of any signs of a movement disorder.

During a holiday trip to Turkey at the age of 3 years and 3 months, the girl suffered from a febrile airway infection. She developed dyspnoea and refused to eat. Her condition rapidly deteriorated and the parents decided to return to Germany for medical treatment. The parents tried to apply maltodextrin solution for anabolisation, but the girl drank only small amounts. During the flight, her consciousness was reduced and she developed haematemesis.

On admission, the girl was somnolent, had fever and presented with tachypnoea. During the initial clinical examination, no signs of a movement disorder were observed. Severe metabolic acidosis was found (pH 7.19, bicarbonate 8.9 mmol/L, base excess −17.7 mmol/L, pCO₂ 23 mmHg) and metabolic emergency treatment was instituted including discontinuation of all protein intake and intravenous administration of high glucose-containing solution, insulin and carnitine. Due to persisting massive tachydyspnoea and increasing respiratory failure, intubation and mechanical ventilation were necessary. Inflammatory parameters were elevated (leukocytes 16.4/nL [normal 5.5–15.5], C-reactive protein 160 mg/L [normal <0.5], procalcitonin 45 µg/L [normal <0.5]), and a chest X-ray indicated pneumonia. *Streptococcus pneumoniae*, serotype 14, was isolated in her blood culture and tracheal aspirate. In tracheal aspirate, rhinovirus could also be detected. The girl was diagnosed with invasive septic infection with *Streptococcus pneumoniae* and received appropriate antibiotic treatment. Of note, the girl had timely received all standard vaccinations including a 13-valent pneumococcal conjugate vaccine covering serotype 14 but apparently had not developed an appropriate immunity for unknown reasons; there were no clinical or laboratory signs of immune deficiency (normal IgG, normal red blood count, no increased frequency of infections prior to the episode described here). However, a specific work-up for immune deficiency was not performed.

Furthermore, the girl suffered from acute renal failure (creatinine 1.68 mg/dL [normal 0.2–0.75], blood urea nitrogen 66 mg/dL [normal 5–17]). Renal ultrasound revealed bilateral swelling, cortical hyperechogenicity and subcortical hypoperfusion. She also had anaemia (haemoglobin 9.6 g/dL [normal 10.1–13.1]) and showed signs of haemolysis (LDH 1,892 U/L [normal 120–300], raised up to 2,837 U/L the following days). Creatine kinase was elevated on admission (827 U/L [normal <148]) but normalised within 2 days, indicating absence of rhabdomyolysis. Platelets were elevated on admission but fell to 40,000/µL (normal 150,000–500,000) on the second day. A blood smear showed schistocytes. This combination of acute renal failure, haemolytic anaemia and thrombocytopenia lead to the clinical diagnosis of atypical haemolytic uraemic syndrome (HUS) associated with pneumococcal disease. Unfortunately, the girl's condition did not allow for renal biopsy to confirm the diagnosis histologically. Analyses of urine revealed a pronounced glomerular and tubular proteinuria (albumin maximum 4,857 mg/g creatinine [normal <30]; alpha-1-microglobulin maximum 193 mg/g creatinine [normal <30]).

Due to a further decline of urine output and increasing renal retention parameters (creatinine maximum 2.99 mg/dL;

cystatine c maximum 3.19 mg/L [normal 0.53–0.95]; GFR calculated from cystatine c minimum 25 mL/min) peritoneal dialysis was started on day 3 of hospitalisation and had to be changed to haemodialysis on day 6. In addition, plasmapheresis was performed several times as an attempt to treat the HUS. Determination of acylcarnitines in dried blood spots during renal failure revealed an elevation of free carnitine (917 μ mol/L [normal 10–70]) and all acylcarnitines, especially glutaryl carnitine (364 μ mol/L [normal <0.4]). Determination of organic acids in urine showed a vastly elevated concentration of lactate (15,025 mmol/mol creatinine [normal <285]) and glutarate (4,839 mmol/mol creatinine [normal <5]), and a slight elevation of concentrations of citric acid cycle intermediates (succinate 203 mmol/mol creatinine [normal <79]; fumarate 34 mmol/mol creatinine [normal <10]) and ketones (2-hydroxybutyrate 271 mmol/mol creatinine [normal <5]; 3-hydroxybutyrate 135 mmol/mol creatinine [normal <11]). 3OHGA was not detectable in this sample. No clinical signs of a movement disorder were detected at any time; however, the validity of neurological exam was restricted due to sedation. The girl's condition did not permit an MRI scan, but on day 13 a cranial CT scan was performed to assess for brain abnormalities. This scan revealed enlarged Sylvian fissures (stable as compared to MRI findings at age 1 month); the basal ganglia did not show any abnormalities. Taken together, neither clinical nor radiographic signs of an encephalopathic crisis were detected.

The clinical course was further complicated by severe lactic acidosis. For a short period of time, reduction of glucose administration had a positive effect. However, lactate concentrations increased again and were persistently elevated above 30 mmol/L for several days, and were refractory to any therapeutic intervention. The girl died 22 days after admission due to multiple organ failure. Post-mortem was declined by the parents.

Discussion

Here, we report on a patient with GA1 and acute renal failure most likely due to atypical HUS caused by invasive pneumococcal disease.

Renal involvement has not been considered to be part of the phenotypic spectrum of GA1 previously. However, it has been shown that 20–25% of adults with GA1 above the age of 20 years suffer from chronic renal failure (Kölker et al. 2015). In addition, there have been single reports about patients with GA1 and renal disease (Table 1). Pöge and colleagues described a patient with GA1 who first presented with neurologic symptoms in the neonatal period and developed nephrotic syndrome at the age of 12 weeks with glomerular damage, crescentic glomerulonephritis but

a normal tubular morphology (Pöge et al. 1997). In another report, a 6-year-old patient with GA1 was described suffering from acute renal failure requiring dialysis. Similar to our case, HUS had initially been suspected in this patient because of accompanying anaemia and thrombocytopenia. However, kidney biopsy in this patient revealed significant acute tubular damage with distended tubules, damaged epithelial cells and loss of the brush border membrane, while the glomeruli were morphologically intact (Pode-Shakked et al. 2014). Interestingly, the tubular morphology reported in this case resembles the renal alterations observed in a mouse model of GA1 during induced metabolic crises (Thies et al. 2013). In the latter study, during metabolic crises induced by the administration of a high protein diet, Gcdh-deficient mice showed an acute tubular damage with functional tubulopathy, a thinning of brush border membranes in renal proximal tubule cells and an altered mitochondrial morphology with enlargement of mitochondria and a reduction in electron density.

In the patient reported here, from the clinical point of view the acute renal failure had been attributed to atypical HUS caused by proven pneumococcal sepsis. Due to the lack of renal histology, however, it cannot be excluded that our patient alternatively or in addition suffered from acute tubular damage as reported earlier in a patient with initial suspicion of HUS (Pode-Shakked et al. 2014), as indicated by the elevated urinary excretion of the tubulopathy marker alpha-1-microglobulin in our patient.

Taken together, it cannot be proven whether the metabolic (GA1) and renal (HUS) diseases in our patient were inter-related or rather independent events. However, the increasing evidence that in GA1 patients chronic renal failure develops over time (Kölker et al. 2015), and single cases of GA1 patients with acute renal diseases as presented here, suggest that the metabolic alterations in GA1 may display a pre-disposing factor for the development of acute and/or chronic renal disease.

Various pathomechanisms may be involved in renal disease in GA1 patients:

1. The pathophysiology of both GA1 and HUS involves microangiopathy: HUS is associated with thrombotic microangiopathy of glomerular endothelium (Noris et al. 2012), whereas in the presence of the GA1-specific metabolite 3OHGA the endothelial integrity was impaired in in vitro and in vivo models of endothelial barriers (Mühlhausen et al. 2006). The impaired endothelial integrity due to the disease-specific metabolites may pre-dispose GA1 patients to HUS-specific microangiopathy as an add-on pathogenic event, thus making GA1 patients more prone to the development of HUS.

Table 1 Functional and histologic renal alterations in GA1 patients

Model	Renal dysfunction	Glomerular histology	Tubular histology	Reference
Case report	Nephrotic syndrome	Crescentic glomerulonephritis: shrinking of glomerular tufts, increased mesangial matrix, extracapillary epithelial proliferations, formation of larger epithelial crescents	Normal	Pöge et al. (1997)
GA1 mouse model	Tubulopathy	Normal	Acute tubular damage: thinned brush border membrane, altered mitochondrial morphology with enlargement and reduced electron density	Thies et al. (2013)
Case report	Acute renal failure, proteinuria, suspected HUS	Normal	Acute tubular necrosis: tubular damage with distended tubules, damaged epithelial cells, loss of brush border, debris in the tubular lumen, interstitial oedema	Pode-Shakked et al. (2014)
E-IMD study population (GA1, $n = 150$; 14% of OAD cohort adult patients)	Chronic renal failure in 25% of adult patients >20 years of age	Not reported	Not reported	Kölker et al. (2015)
Case report	Acute renal failure, suspected HUS; proteinuria (albumin, alpha-1-microglobulin)	Not done	Not done	This report

- Renal proximal tubule cells express various transporters that mediate the urinary excretion of GA and 3OHGA (Hagos et al. 2008; Mühlhausen et al. 2008; Stellmer et al. 2007); the expression of these transporters is altered during induced metabolic crises in a GA1 mouse model, which may result in an intracellular accumulation of GA and 3OHGA in renal proximal tubule cells, contributing to an impairment of mitochondrial energy production in these cells (Thies et al. 2013). Thus, a severely catabolising condition such as an invasive pneumococcal disease may lead to metabolic decompensation and an increase of GA and 3OHGA concentrations in proximal tubule cells. This may promote a continuously progressive renal proximal tubule dysfunction, eventually leading to acute tubular damage and renal failure. In addition, non-acute but chronic exposure of renal proximal tubule cells to GA and 3OHGA may account for the chronic development of a tubular disease and eventually chronic renal failure as reported in adult GA1 patients. The potential role of renal proximal tubule cells in the development of GA1-associated renal disease is in line with recent

observations of a high renal GCDH expression specifically in proximal tubule cells (Braissant et al. 2017).

Conclusion

This case report adds to the growing evidence of acute and chronic renal disease in GA1 triggered by acute catabolic events or developing over time, respectively. Further research is necessary to unravel the underlying mechanisms. With regard to patient care, we consider it important to carefully monitor glomerular as well as tubular function in GA1 patients to detect a potential impairment of renal function as early as possible.

Synopsis

We report on a 3-year-old GA1 patient with acute renal failure most likely due to haemolytic uraemic syndrome associated with a pneumococcal infection. Endothelial dysfunction and renal proximal tubule accumulation of

GA1 metabolites may contribute to acute and chronic glomerular and tubular dysfunction in GA1 patients.

Compliance with Ethics Guidelines

Conflict of Interest Statement

Marcel du Moulin, Bastian Thies, Martin Blohm, Jun Oh, Markus J. Kemper, René Santer and Chris Mühlhausen declare that they have no conflict of interest.

Informed Consent

The study does not contain any identifying information about patients.

This chapter does not contain any studies with human or animal subjects performed by any of the authors.

Details of the Contributions of Individual Authors

Marcel du Moulin: Dr. du Moulin cared for the patient, performed collection and analyses of the data, drafted and critically reviewed the manuscript and approved the final manuscript as submitted.

Bastian Thies: Dr. Thies cared for the patient, performed collection and analyses of the data, drafted and critically reviewed the manuscript and approved the final manuscript as submitted.

Martin Blohm: Dr. Blohm cared for the patient, especially with regard to the intensive care management, carried out critical discussions regarding the pathophysiology of the patient, collected and analysed the data, reviewed and revised the manuscript and approved the final manuscript as submitted.

Jun Oh: Dr. Oh carried out and critically discussed the nephrologic treatment of the patient (dialysis procedures), collected and critically discussed the data, reviewed and revised the manuscript and approved the final manuscript as submitted.

Markus J. Kemper: Dr. Kemper carried out and critically discussed the nephrologic treatment of the patient (dialysis procedures), collected and critically discussed the data, reviewed and revised the manuscript and approved the final manuscript as submitted.

René Santer: Dr. Santer carried out and critically discussed the metabolic treatment of the patient, critically analysed and reviewed the collected data, drafted, critically reviewed and revised the manuscript and approved the final manuscript as submitted.

Chris Mühlhausen: Dr. Mühlhausen carried out, critically discussed and reviewed the metabolic treatment of the patient, designed the data collection instruments, coordinated and supervised data collection and analyses, drafted and critically reviewed the manuscript and approved the final manuscript as submitted.

References

- Baric I, Wagner L, Feyh P, Liesert M, Buckel W, Hoffmann GF (1999) Sensitivity and specificity of free and total glutaric acid and 3-hydroxyglutaric acid measurements by stable-isotope dilution assays for the diagnosis of glutaric aciduria type I. *J Inher Metab Dis* 22:867–882
- Boy N, Mühlhausen C, Maier EM et al (2017) Proposed recommendations for diagnosing and managing individuals with glutaric aciduria type I: second revision. *J Inher Metab Dis* 40:75–101
- Braissant O, Jafari P, Remacle N, Cudré-Cung H-P, do Vale Pereira S, Ballhausen D (2017) Immunolocalization of glutaryl-CoA dehydrogenase (GCDH) in adult and embryonic rat brain and peripheral tissues. *Neuroscience* 343:355–363
- Goodman SI, Frerman FE (2001) Organic acidemias due to defects in lysine oxidation: 2-ketoadipic acidemia and glutaric acidemia. In: Scriver CR, Beaudet AL, Sly WS et al (eds) *The metabolic and molecular bases of inherited disease*. McGraw-Hill, New York, pp 2195–2204
- Hagos Y, Krick W, Bräulke T, Mühlhausen C, Burckhardt G, Burckhardt BC (2008) Organic anion transporters OAT1 and OAT4 mediate the high affinity transport of glutarate derivatives accumulating in patients with glutaric acidurias. *Pflugers Arch* 457:223–231
- Jafari P, Braissant O, Bonafé L, Ballhausen D (2011) The unsolved puzzle of neuropathogenesis in glutaric aciduria type I. *Mol Genet Metab* 104:425–437
- Keyser B, Glatzel M, Stellmer F et al (2008) Transport and distribution of 3-hydroxyglutaric acid before and during induced encephalopathic crises in a mouse model of glutaric aciduria type I. *Biochim Biophys Acta* 1782:385–390
- Kölker S, Valayannopoulos V, Burlina AB et al (2015) The phenotypic spectrum of organic acidurias and urea cycle disorders. Part 2: The evolving clinical phenotype. *J Inher Metab Dis* 38:1059–1074
- Lamp J, Keyser B, Koeller DM, Ullrich K, Bräulke T, Mühlhausen C (2011) Glutaric aciduria type I metabolites impair the succinate transport from astrocytic to neuronal cells. *J Biol Chem* 286:17777–17784
- Mühlhausen C, Ott N, Chalajour F et al (2006) Endothelial effects of 3-hydroxyglutaric acid: implications for glutaric aciduria type I. *Pediatr Res* 59:196–202
- Mühlhausen C, Burckhardt BC, Hagos Y et al (2008) Membrane translocation of glutaric acid and its derivatives. *J Inher Metab Dis* 31:188–193
- Noris M, Mescia F, Remuzzi G (2012) STEC-HUS, atypical HUS and TTP are all diseases of complement activation. *Nat Rev Nephrol* 8:622–633
- Pode-Shakked B, Marek-Yagel D, Rubinshtein M et al (2014) Glutaric aciduria type I and acute renal failure – coincidence or causality? *Mol Genet Metab Rep* 1:170–175
- Pöge AP, Autschbach F, Korall H, Trefz FK, Mayatepek E (1997) Early clinical manifestation of glutaric aciduria type I and nephrotic syndrome during the first months of life. *Acta Paediatr* 86:1144–1147

- Sauer SW, Okun JG, Fricker G et al (2006) Intracerebral accumulation of glutaric and 3-hydroxyglutaric acids secondary to limited flux across the blood-brain barrier constitute a biochemical risk factor for neurodegeneration in glutaryl-CoA dehydrogenase deficiency. *J Neurochem* 97:899–910
- Stellmer F, Keyser B, Burckhardt BC et al (2007) 3-Hydroxyglutaric acid is transported via the sodium-dependent dicarboxylate transporter NaDC3. *J Mol Med* 85:763–770
- Thies B, Meyer-Schwesinger C, Lamp J et al (2013) Acute renal proximal tubule alterations during induced metabolic crises in a mouse model of glutaric aciduria type 1. *Biochim Biophys Acta* 1832:1463–1472