Collapsing glomerulopathy in a child with LCHAD deficiency: a rare association

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Abstract

Metabolic disorders, although rare, can involve multiple organ systems and have a varied presentation. Renal involvement has been reported in several metabolic disorders in the pediatric age group. We report a rare metabolic disorder, long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency, in a child who developed steroid-resistant nephrotic syndrome at the age of 5 years. Renal biopsy showed features of collapsing glomerulopathy. The child had progressive chronic kidney disease. Alternative immunosuppressants including tacrolimus failed to show any clinical improvement. There have been no reports of children with long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency developing steroid-resistant nephrotic syndrome and collapsing glomerulopathy. This case highlights the need to monitor renal function and proteinuria among this group of children.

Keywords Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency · Child · Nephrotic syndrome · Collapsing glomerulopathy

Background

Metabolic disorders, although rare, can involve multiple organ systems and have a varied presentation. Renal involvement has been reported in several metabolic disorders in the pediatric age group. One such metabolic disorder is long-chain 3-hydroxyacyl-CoA dehydrogenase (LCHAD)

deficiency. Renal involvement as acute kidney injury secondary to decompensation has been previously reported in the literature. Our case highlights, for the first time, a rare presentation of steroid-resistant nephrotic syndrome in a child with LCHAD deficiency and histopathology of collapsing glomerulopathy.

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Case presentation

A 5-year-old boy of Pakistani origin, born at term to consanguineous parents, was followed since birth at the pediatric metabolic disease clinic and was referred to the pediatric nephrology unit for evaluation of new onset nephrotic range proteinuria. Clinical examination showed an averagely nourished child with mild pallor. He had periorbital and pedal edema. His laboratory investigations showed creatinine of 18 $\mu\text{mol/L}$ (normal range 21–42), urea 3.80 mmol/L (2.80–8.10), albumin 16 g/L (35–52), total cholesterol 6.28 mmol/L (2.80–4.80), hemoglobin 95 g/L (110–140), and neutrophil count 2000/mm³. The urine protein to creatinine ratio was 3.86 g/g while urine albumin was 4+ and erythrocytes were 1+. Complement, antinuclear antibody, and anti-double stranded DNA antibody levels were normal.

He was born through full-term vaginal delivery with a birth weight of 3 kg and no post-natal complications. His past medical history was significant for LCHAD deficiency which was detected as a part of routine newborn screening, and the diagnosis was confirmed by demonstration of persistent elevation in several long-chain hydroxy-acylcarnitines in plasma, especially the concentration of 3-hydroxy palmitoylcarnitine which was markedly elevated. His plasma total and free carnitine levels as well as urine organic acid analysis were always normal. The prominent accumulation of 3-hydroxy species was consistent with a diagnosis of either LCHAD deficiency or mitochondrial trifunctional protein (MTP) deficiency. Subsequently, he was managed with a long-chain fat restricted diet by provision of a medium-chain triglyceride formula (Monogen). The family was educated to avoid any possible metabolic decompensations during intercurrent illnesses with an emergency management plan.

At 4 weeks of age, he was admitted due to hypocalcemic seizures. Laboratory tests showed high phosphorous, low 25-hydroxy-vitamin D with normal parathyroid hormone (PTH) levels, and mild metabolic acidosis. There was no evidence of metabolic decompensation as evident from normal blood glucose, creatine kinase, and liver enzymes. Of note, PTH was suppressed despite low calcium and high phosphate levels. The association of MTP deficiency with hypoparathyroidism was considered. He had recurrence of the hypocalcemic seizures after 2 weeks which were managed conservatively.

Genetic testing including *HADHA* and *HADHB* gene sequencing as well as deletion–duplication analysis to confirm the diagnosis was negative in the first year of life.

He continued to be followed up at the pediatric metabolic disease clinic and routine surveillance for possible LCHAD deficiency-related complications was performed with yearly ophthalmologic and cardiologic evaluations. This was aimed to detect retinopathy or cardiomyopathy and arrhythmias. To date, none has been observed.

Over the years, he had multiple admissions for febrile illnesses, and during one episode he had transient elevation in creatine kinase as well as high plasma lactate levels. However, his blood glucose remained consistently normal.

During regular follow-up visits at around 2 years of age, he was found to have anemia (hemoglobin 80 g/L) as well as neutropenia (absolute neutrophil count 800/mm³). Peripheral blood showed moderate hypochromic anemia and moderate neutropenia. The iron profile showed a serum ferritin level of 410 mcg/L (13–110) and a transferrin saturation of 0.93 (0.11–0.54). A trial of iron treatment failed to improve the anemia. Therefore, the hematology team was consulted for persistent anemia not responding to iron supplements and they elected to proceed with a bone marrow evaluation. This revealed a cellular and normoblastic bone marrow with tri-lineage hematopoiesis and left shift in granulopoiesis. There

were no signs of storage disease, increase in blast cells, or significant dysplastic changes. Iron stores were slightly decreased. Occasional ringed sideroblasts were noted representing < 15% of nucleated red blood cells. Plasma erythropoietin levels were high at 100 IU/L (3.7–36). High performance liquid chromatography (HPLC) was consistent with a heterozygous state of Hb D-Los Angeles (D-Punjab).

Pyridoxine was started since the bone marrow showed sideroblasts although the percentage of ring sideroblasts was not consistent with the definitive diagnosis of sideroblastic anemia. This, however, was not very successful in improving his anemia. A repeat bone marrow was planned but was declined by the family.

At 5 years of age, he was evaluated for nephrotic syndrome and initiated on steroids. He showed primary steroid resistance and hence a renal biopsy was performed which was suggestive of collapsing glomerulopathy (Fig. 1). The renal biopsy showed 32 glomeruli including 2 globally sclerosed. Five glomeruli showed “collapsing features” of the tufts globally or segmentally, with associated mild to moderate proliferation and hypertrophy of the visceral podocytes. The capillary walls showed irregularities and corrugation especially in the tufts neighboring the collapsing areas. Mild diffuse tubular injury and patchy areas of interstitial fibrosis and tubular atrophy were seen involving approximately 15–25% of the entire cortical areas. The arterioles showed moderate intimal thickening and sclerosis. On immunofluorescence microscopy, there was focal and segmental fine granular staining of the mesangial area for IgG(1–2+), IgM(2+), C3(2–3+), C1q(1–2+), kappa light chain (1+), and lambda light chain (2–3+). Electron microscopy showed many areas of the glomerular basement membrane (GBM) having irregularities in the form of corrugation, splitting, and extensive mesangial cell

Fig. 1 Renal biopsy. Jones stain (×400) showing a globally collapsing glomerulus with proliferating visceral podocytes

interposition. The podocytes were considerably enlarged with an increase of intracytoplasmic protein droplets and severe, near total, podocytes foot process effacement involving almost 100% of the entire capillary surface. No recognized tubulo-reticular inclusions in endothelial cells or mitochondrial changes were seen. Intracytoplasmic vacuolization was seen in some tubular cells.

Human immunodeficiency virus (HIV) testing was negative. Genetic evaluation for genes responsible for steroid-resistant nephrotic syndrome was also negative. The child received a trial of tacrolimus but this was stopped due to non-response and worsening of renal function.

Whole genome sequencing re-analysis revealed a novel homozygous deep-intronic variant of uncertain significance in the *HADHA* gene (Table 1). Functional RNA studies were recommended to determine whether the variant has any effect on splicing but could not be done due to financial limitations.

His current weight and height are on the tenth percentile and he continues to follow the same growth curve since childhood. His cardiac and ophthalmological evaluations at 5 years of age remain normal and do not show any abnormality.

He is maintained on chronic kidney disease management. Currently his cystatin C estimated glomerular filtration rate (eGFR) is 30 mL/min. His current medications include angiotensin-converting-enzyme inhibitors and calcium channel blockers. He continues to have anemia. His hemoglobin remains in the range of 70–80 g/L during which he is on iron and folic acid supplementation as well as pyridoxine and erythropoiesis-stimulating agents. His liver enzymes remain normal.

Discussion

LCHAD and MTP deficiencies are disorders attributed to different defects in the MTP. MTP is an enzyme complex in the inner mitochondrial membrane with three enzymatic activities, LCHAD, 2-enoyl hydratase, and 3-keto acyl-CoA thiolase. Both isolated LCHAD deficiency and MTP deficiency, which includes deficiencies in all three enzymatic activities, have overlapping clinical presentations. The variable presentation includes infantile hypoketotic hypoglycemia, vomiting, lethargy, hypotonia, and failure to thrive. Additional presentations include cardiomyopathy and cardiac conduction defects, severe liver disease, recurrent muscle cramps, seizures, coma, or sudden death. Patients may have acute decompensations with intercurrent illnesses, decreased oral intake, prolonged fasting episodes, surgical requirement, among others which usually necessitate frequent hospitalizations. Peripheral neuropathy and pigmentary retinopathy may also develop at a later age [1].

LCHAD deficiency is a rare autosomal recessive inborn error of metabolism, in which the mitochondrial enzymes required for the breakdown of fatty acids to produce energy are deficient and, therefore, individuals with this enzyme deficiency are unable to break down long-chain fatty acids. This results in the long-term accumulation of 3-hydroxy-long-chain species as well as energy deficiency during intercurrent illness, which may lead to hypoketotic hypoglycemia as well as possible muscle, liver, and cardiac dysfunctions of variable severity.

Confirmatory testing is done through plasma acylcarnitine profile analysis. Patients affected with LCHAD deficiency commonly show increased hydroxycompounds: C14-OH, C16-OH, C18-OH, and C18:1-OH. Analysis of organic acids in urine usually demonstrates C6–C14

Table 1 Genetic testing of index child

Gene	Variant coordinates	Zygosity	In silico parameters ^a	Allele frequencies ^b	Type and classification ^c
HADHA	Chr2(GRCh37):g.26418240G>C NM_000182.4:c.1480-139C>G Intron 14	Homozygous	PolyPhen: N/A Align-GVGD: N/A SIFT: N/A MutationTaster: N/A Conservation: nt weak	gnomAD ESP 1000 G CentoMD	Substitution Uncertain significance (class 3)

Variant description based on Alamut Batch (latest database available)

The HADHA variant c.1480-139C>G results in a substitution intron 14. The nucleotide is not conserved and in silico predictions do not indicate any effect on splicing (Alamut 2.10); however, given that the variant is novel and highly suggestive biochemical data, it is classified as variant of uncertain significance (class 3) according to the recommendations of Centogene and ACMG

^aAlignGVGD: C0: least likely to interfere with function, C65: most likely to interfere with function, splice prediction tools: SSF, MaxEnt, HSF

^bGenome Aggregation Database (gnomAD), Exome Sequencing Project (ESP), 1000Genome project (1000G) and CentoMD[®] (latest database available)

^cBased on ACMG recommendations

hydroxy-dicarboxylic acids. MTP deficiency is associated with hypoparathyroidism [2, 3] as seen in our index child.

Treatment is life-long and includes avoidance of fasting, carnitine supplementation (if carnitine levels are low), as well as a long-chain fat-restricted diet. Prompt detection and treatment of any metabolic crises with high dextrose containing intravenous fluids are necessary to prevent complications.

Potential renal involvement during acute metabolic decompensations may lead to acute kidney injury due to rhabdomyolysis. To date, however, there have been no reports of an association between LCHAD deficiency and chronic renal involvement such as collapsing glomerulopathy. In general, metabolic disorders that are most frequently associated with renal manifestations include lysosomal storage disorders, organic acid disorders, fatty acid oxidation disorders, peroxisomal disorders, disorders of purine and pyrimidine metabolism, and carbohydrate disorders. The specific metabolic disorders associated with steroid-resistant nephrotic syndrome include alpha-1-antitrypsin deficiency, Fabry disease, glutaric aciduria, glycogen storage disease, Hurler syndrome, lipoprotein disorders, and mitochondrial cytopathies. Mitochondrial disorders can have renal involvement in the form of proximal tubulopathy, nephrotic syndrome, renal failure, and tubulointerstitial nephritis.

Collapsing glomerulopathy is rarely encountered in children and presents with steroid-resistant nephrotic syndrome with a rapid progressive course leading to end-stage renal disease. It is a clinically and pathologically distinct variant of focal segmental glomerulosclerosis (FSGS) and has been recognized in the absence of HIV infection. The etiology of this enigmatic disorder is still elusive, but a growing list of diseases/conditions is being reported in association with this typical morphological pattern of renal parenchymal injury. Two major common pathways have been proposed to explain the stereotyped response of the renal parenchyma to a variety of triggering/injurious agents in collapsing glomerulopathy: activation of the immune system and the dysregulation of mitochondrial function [4]. The possible pathogenesis of collapsing glomerulopathy in our index child could be due to abnormality of the mitochondrial function.

Gulati and colleagues evaluated six children with idiopathic collapsing glomerulopathy and steroid-resistant nephrotic syndrome, with or without azotemia, was the presenting clinical feature in all cases. Immunosuppressive therapy was able to achieve complete remission of proteinuria (one patient), partial remission (four patients), or no change in proteinuria (one patient). Two of the six patients progressed to end-stage renal disease within a median follow-up period of 27 months [5]. Kari and colleagues reported an 18-month-old child with collapsing glomerulopathy who presented with steroid-resistant nephrotic syndrome and progressed early to end-stage renal failure [6].

Collapsing glomerulopathy may be classified into three categories such as idiopathic, genetic or reactive forms [7]. It has been reported in children with mitochondrial disorders. Barisoni and colleagues reported an 18-month-old boy who had coenzyme Q2, polyprenyltransferase, associated collapsing glomerulopathy. It was suggested that collapsing glomerulopathy associated with a mutation in a nuclear gene encoding mitochondrial proteins may be a rare condition; however, screening for mitochondrial morphology remains essential in patients with unexplained proteinuria [8]. Our index child presented with steroid-resistant nephrotic syndrome with collapsing features on renal biopsy on a background of biochemical LCHAD deficiency.

Our report is the first to document an association of LCHAD deficiency and glomerulopathy. It may be suggested that children with LCHAD deficiency should be screened for proteinuria and followed for alterations in renal function as a monitoring tool.

Author contributions GK planned, conducted, and reported the work described in the article. RN was involved in conception and design of the case report. GK and RN clinically managed the child. BSH reviewed the histopathology slides of renal biopsy. OAA, AAA, AMAA drafted the article. AMJA critically reviewed the manuscript. AT will act as guarantor of the paper.

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Compliance with ethical standards

Conflict of interest All Authors declare that they have no conflict of interest.

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