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CONGENITAL NEPHROTIC SYNDROME IN AN INFANT WITH *ALG1*-CONGENITAL DISORDER OF GLYCOSYLATION

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Abstract

Congenital nephrotic syndrome in the newborn is most frequently related to mutations in genes specific for structural integrity of the glomerular basement membrane and associated filtration structures within the kidney, resulting in massive leakage of plasma proteins into the urine. Occurrence of congenital nephrotic syndrome in a multi-system syndrome is less common. We describe an infant with deteriorating neurological status, seizures, edema, and proteinuria who was found to have a mutation in *ALG1* and a renal biopsy consistent congenital nephrotic syndrome. Furthermore, we briefly review rare existing case reports documenting congenital nephrotic syndrome in patients with *ALG1* and treatment strategies, including novel use of peritoneal dialysis.

Keywords

edema; hypoalbuminemia; fluid overload; peritoneal dialysis; microcephaly; pontocerebellar atrophy

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Transparency Declarations

The authors have no conflicts of interest to disclose. The genetic sequencing information presented in this paper has been described in reference 10.

Institutional Review Board at our institution deemed that informed consent was not required for the purposes of this case report.

Introduction

Congenital nephrotic syndrome describes a clinical entity of edema, hypoalbuminemia, hyperlipidemia, and proteinuria within the first three months of life. The majority of congenital nephrotic syndrome cases are primary and due to mutations in *NPHS1* (nephrin), *WT1* (Wilms tumor suppressor), or *NPHS2* (podocin) genes leading to derangement of the glomerular basement membrane and filtration apparatus with resultant proteinuria. In the perinatal period, this disorder can present as a component of a multi-system, generalized syndrome. In particular, congenital nephrotic syndrome has been reported to occur concurrently with failure to thrive, microcephaly, deteriorating neurological status, and sepsis in the setting of congenital disorders of glycosylation due to mutations in the *ALG1* gene [1–6, 10].

Congenital disorders of glycosylation (CDG) are rare multisystem diseases due to impaired synthesis, transfer, and processing of sugars resulting in hypoglycosylation of ubiquitously expressed proteins throughout the body [7]. The congenital disorder of glycosylation associated with *ALG1* (*ALG1*-CDG) gene mutations (OMIM #608540) is described as an inherited error of metabolism resulting in deficiency of β-1,4 mannosyltransferase (OMIM #605907). The *ALG1*-CDG phenotype is characterized by microcephaly, developmental delay, abnormal fat distribution, strabismus, and coagulation abnormalities [8]. *ALG1*-CDG has also been associated with recurrent infantile seizures, cerebellar hypoplasia, hypotonia, and failure to thrive. There are 58 described cases of *ALG1*-CDG in the existing literature with twelve of those cases also reporting the presence of renal failure and congenital nephrotic syndrome [2, 8, 9, 10]. We report details of one case of congenital nephrotic syndrome associated with *ALG1*-CDG, formerly known as CDG type 1k, and discuss the use of peritoneal dialysis in management of this rare patient population.

Case Presentation

The infant (patient # 18, reference [10]) was a full term male, born at a community hospital. Due to recurrent apnea, feeding difficulties, and *Enterobacter cloacae* sepsis, he was transferred to neonatal intensive care unit at one month of age. He was the first child of healthy, non-consanguineous parents with unremarkable family history. Examination at admission was notable for microcephaly, hypertelorism, weak gag reflex, hypotonia, clenched hands, shortened limbs, bilateral cryptorchidism, and sacral dimple with a tuft of hair. Medical history from was notable for hypertension, mild generalized edema, and poor nutritional status. He was hypoalbuminemic (1.1 g/dL) with proteinuria (urine protein to creatinine ratio of 14.0) and microscopic hematuria (30 red blood cells per high power field).

The infant became progressively edematous and oliguric with persistent hypoalbuminemia requiring albumin replacement. Due to progressive renal dysfunction, a renal biopsy was performed. The biopsy revealed complete podocyte effacement without mesangial sclerosis and unremarkable immunofluorescence, suggestive of congenital nephrotic syndrome (Figures 1 and 2). He developed worsening fluid overload that became refractory to albumin and furosemide, and a peritoneal dialysis catheter was placed to provide mechanism for ultrafiltration and liberalization of total fluids due to the infant’s poor nutritional state.

His neonatal course was further complicated by neurological, growth, and infectious complications. He had progressive neurological deterioration with seizures refractory to multiple anti-epileptic medications and required continuous ventilatory support due to recurrent seizure-related apnea. Magnetic resonance imaging revealed pontocerebellar atrophy with an absent cerebellar vermis and small posterior fossa. The infant experienced failure to thrive despite optimized enteral and parenteral nutrition. Enteral feeding was complicated by recurrent aspiration, requiring Nissen fundoplication. In addition to *Enterobacter cloacae* sepsis at the time of transfer, the infant had *Stenotrophomonas maltophilia* sepsis during his hospital course. In the setting of hypogammaglobulinemia (IgG 77 mg/dL) and congenital nephrotic syndrome, intravenous immunoglobulin was provided in addition to antibiotic therapy for sepsis therapy.

At three months of age, the decision was made to transition to palliative care. The infant demonstrated rapidly worsening respiratory and renal failure, and life-sustaining measures were withdrawn. The infant died at three months of age.

Genetic and metabolic disorders were investigated as causative etiologies for the infant's clinical presentation of pontocerebellar atrophy, seizures, and renal failure encompassing a broad disease differential, including congenital disorders of glycosylation. Chromosome microarray demonstrated a copy number variant (167 kb duplication on 9q32) not currently associated with a human constitutional disorder. Carbohydrate-deficient transferrin analysis was performed by electrospray ionization mass spectrometry. This showed elevation in the CDG mono/di ratio (mono/di = 2.151) and CDG A/DI oligosaccharide ratio (A/DI = 1.772), suggestive of a CDG type I pattern. Molecular testing for CDG-Ia (*PMM2*) and CDG-Ib (*MPI*) was negative for mutations in genes known to cause disease; however, post-mortem, research-based whole exome and Sanger sequencing confirmed patient homozygosity for a known CDG causing mutation in *ALG1*, specifically a c.773C>T substitution that causes a missense mutation p.S258L (dbSNP ID - rs28939378), causative for *ALG1*-CDG. This was confirmed by a CLIA certified lab (GeneDx).

Discussion

ALG1-CDG is a rare but recognized cause of congenital nephrotic syndrome. There is considerable overlap in phenotype due to isolated congenital nephrotic syndrome and congenital nephrotic syndrome in the setting of *ALG1*-CDG. Specifically, both diseases are notable for significant failure to thrive, coagulopathy and increased risk for severe bacterial infections [8, 11]. *ALG1*-CDG should be considered in the differential diagnosis of congenital nephrotic syndrome, particularly if patient presentation involves neurological deterioration.

Recent genetic analysis of six individuals with ALG1 mutations and renal failure demonstrated homozygosity for S258L [10]. Furthermore, there are six additional cases of congenital nephrotic syndrome associated with *ALG1*-CDG (Table 1). Range of patient age at onset of nephrotic syndrome was 3 weeks to 15 months. Some reports describe lifespan of patients with *ALG1*-CDG extending into adolescence or early adulthood; however, all reported cases of *ALG1*-CDG associated with nephrotic syndrome experienced death before

2 years of age [1, 3, 5, 6, 8]. Pathology from renal biopsies described in the literature report diffuse mesangial sclerosis as a prominent biopsy feature in two of the cases [1, 3], in contrast to our patient who had only podocyte effacement.

Hypoalbuminemia, typically without generalized edema, has been described in congenital disorders of glycosylation but may more often be attributed to malnutrition and/or gastrointestinal protein losses [12]. Given the relatively high occurrence of congenital nephrotic syndrome (N = 12/58 or 21% of reported cases of *ALG1*, including our patient), the question could be raised whether surveillance for proteinuria is warranted to ascertain whether hypoalbuminemia is not from urinary losses.

Management options in this rare population are limited. Existing reports describe use of albumin and loop diuretic, fluid restriction, and/or no specific therapy described at all. One case report describes use of angiotensin converting enzyme inhibitor therapy in combination with diuretics for a patient [1]. This is the first report to document the use of peritoneal dialysis in an infant affected by *ALG1*-CDG. This modality allowed for improved fluid management and provision of nutrition in the setting of nephrotic syndrome. Ultimately, management of this unique population may prove difficult even with maximal medical renal therapy as described here given the neurological manifestations of disease, risk for coagulopathy, sepsis, and ultimately high mortality rate in infancy.

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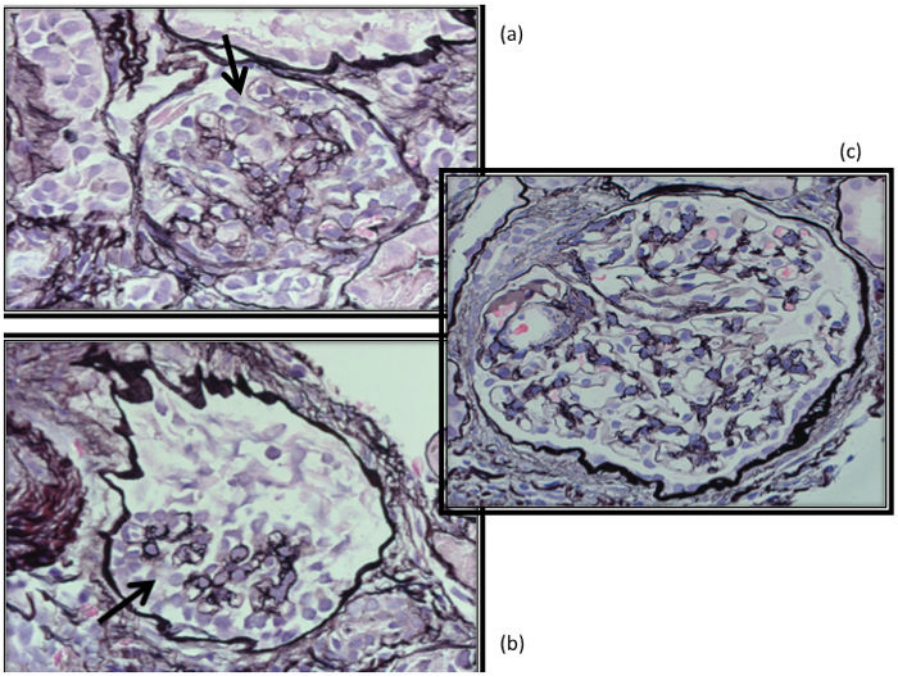

Figure 1.

Two glomeruli (insets A, B) with features of collapsing focal segmental glomerulosclerosis on silver stain. There is epithelial (podocyte) hyperplasia (at arrows) with collapsed capillary loops. Compare with a normal glomerulus (inset C) in photo on the right.

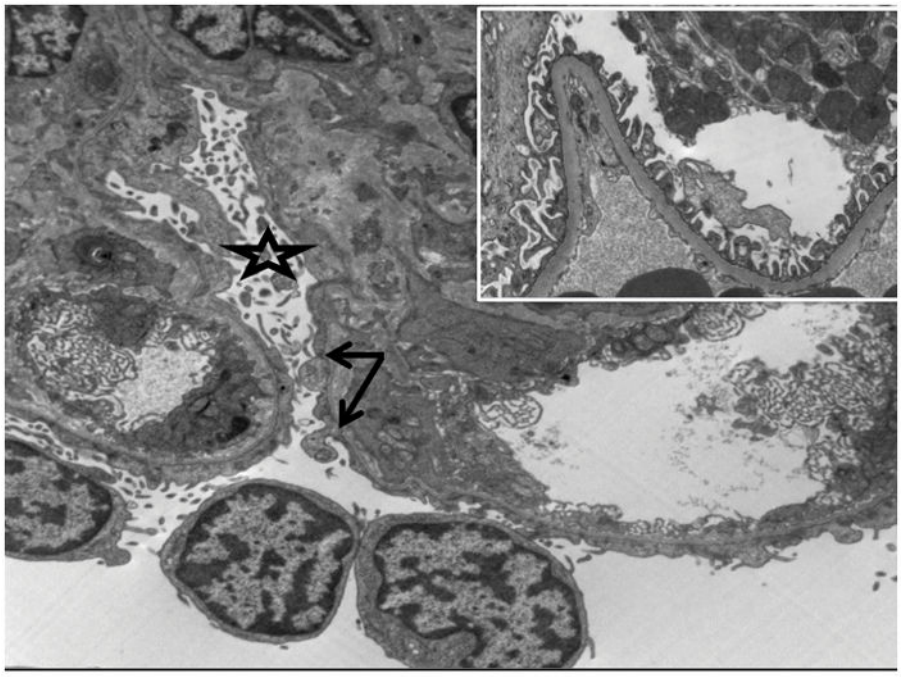

Figure 2.

Electron microscopy demonstrating epithelial (podocyte) foot process effacement with arrow denoting rare intact podocytes and star demonstrating podocyte effacement and microvillous transformation. Comparison electron microscopy depicting a normal glomerulus with intact epithelial (podocyte) foot processes shown at inset.

Table 1

Summary of congenital nephrotic syndrome cases reported to date within pediatric literature. There are seven currently characterized cases of congenital nephrotic syndrome, including the current case.

Author	Age of Onset Nephrotic Syndrome	Renal Pathology	Genetics	Age at Death
Hutchesson (1995)	3 week	Not performed	CDG-I	3 months
Van der Knapp (1996)	< 2 months	Diffuse mesangial sclerosis	CDG-I, phosphomannomutase-2	2 months
De Vries (2000)	< 1 month	Fusion of podocyte foot processes	CDG-I, unknown type	2 months
Kranz (2004)	Not described	Not described	CDG-Ik (ALG1)	11 weeks
Morava (2008)	Not described	Not described	CDG-Ik (*ALG1*)	5 months
Sinha (2009)	15 months	Diffuse mesangial sclerosis	CDG-Ix	17 months