

Congenital Nephrotic Syndrome : A Case Report and Review of Literature

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Abstract: Nephrotic syndrome presenting in the first three months of life is called congenital nephrotic syndrome. The two main causes of this syndrome are congenital nephrotic syndrome of the Finnish type and diffuse mesangial sclerosis, which are both inherited by autosomal recessive transmission. Both are associated with profound growth failure and death from infection during infancy. Prolonged survival can be achieved by early aggressive medical management, nephrectomy, and renal replacement treatment with dialysis and transplantation.

INTRODUCTION

Nephrotic syndrome is a renal disease with proteinuria (> 3 g/d), hypoalbuminemia, and edema. Congenital nephrotic syndrome (<3months) might be secondary to intrauterine infections or an autosomal recessive condition; the Finnish variety presents commonly at this age. Minimal change disease (MCD) is seen between 2-6 yrs; focal segmental glomerulosclerosis (FSGS) may occur throughout childhood, (< 8 yrs) and membranoproliferative glomerulonephritis is seen in older children and adolescents. We present a case of congenital nephrotic syndrome.

CASE REPORT

A 55 day old boy was brought to the triage of Max Superspeciality Hospital with complaints of recurrent episodes of breath holding on crying along with cyanosis noticed by mother since the last 10 -12 days. These episodes had increased over the subsequent 5-6 days (from 1-2/day to 8-10/day) and now included tonic posturing and uprolling of the eye balls. Child was brought to the PICU and was electively intubated and ventilated in view of status epilepticus and impending respiratory failure. On examination the child was sick; VITALS: HR =174/min; RR =60/min; BP = 83/43/52 mmHg; SpO₂ = 90 %. Invasive lines were placed for hemodynamic monitoring. Birth history: Borderline term baby delivered at private hospital by caesarean section; birth weight 2.5 kg; no antenatal problem. Family history: Elder male sibling expired at age of 3 months (preterm 1.4 kg B.wt? severe sepsis); subsequent girl child 6 yr old healthy. His admission blood gas showed very low ionized calcium (1.78 mg %); total Ca=6.1mg% along with severe metabolic derangements i.e. hyponatremia (Na=124meq/L); hypokalemia (K=2.7meq/L); normal anion gap metabolic acidosis (ABG: 7.1/51/58/13.5/-15.5; lactate =4.3mmol) and a positive urinary anion gap. A provisional diagnosis of Renal Tubular Acidosis with hypocalcaemic status epilepticus was initially kept. The initial sepsis profile was negative (including lumbar puncture). His blood reports showed severe hypoalbuminemia (S. albumin = 1.0 g/dL) with albuminuria of 2+ and normal urea and creatinine (8.3mg/dL & 0.1mg/dL respectively). He was worked up for nephrotic syndrome and a diagnosis of congenital nephrotic syndrome was made. His serum cholesterol = 225mg%, C3=91.2mg/dL and C4=25.3mg/dL. His urinary protein/creatinine ratio was markedly elevated (49.1; normal<0.5). Pediatric nephrologist was involved and a renal biopsy was planned for histopathological diagnosis. He was given IV Fluids, IV antibiotics, IV calcium, IV phenobarbitone and therapeutic vitamin D. He was given multiple transfusions of 20% albumin along with lasix during the time he was critical on ventilator. Serum levels of TORCH IgM were WNL. His chest x-ray showed bilateral upper zone collapse for which a fiberoptic bronchoscopy was done, airways cleared and a lavage sent (negative at 48 hrs). His coagulation profile was deranged so renal biopsy could be done on day 7 of admission. He was gradually weaned off the ventilator and extubated after 8 days. Post biopsy he was started on oral ACE inhibitors. His thyroid profile revealed hypothyroidism hence oral thyronorm was added. His metabolic profile improved and he was discharged on oral calcium supplements and ACE inhibitors after 11 days of hospitalization. His renal biopsy report revealed: **glomerulopathy with diffuse mesangial hypercellularity (> 60%) with focal sclerosis.**

The child has been in regular follow up with a pediatric nephrologist; was given a trial of oral steroids. He did show some initial decrease in albuminuria; but thereafter albuminuria persisted. Gene studies in the child and parents were done; which revealed 2 mutations; one novel mutation in the NPHS1 gene (inherited from mother) and second known mutation in another exon in the NPHS1 gene (inherited from father); and each of the parents had the respective mutation as inherited by the baby.

The official report of the child is as follows:

1. NPHS2 and WT1 sequencing is normal

2. NPHS1 gene sequencing results are as follows:

The direct sequencing of all 29 exons of the NPHS1 gene (Nephrin, NM_004646.3) in the above mentioned patient showed the following result:

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NPHS1 Mutation (nucleotide change)	Zygosity	Inherited from
Exon 1: c.41T>C (novel mutation)	Heterozygous	Mother
Exon 27: c.3478C>T [Lenkkeri <i>et al.</i> (1999). <i>Am J Hum Genet</i> 64:51-61] A known Pathogenic mutation	Heterozygous	Father

REVIEW OF LITERATURE

Congenital nephrotic syndrome (CNS) refers to babies who present at birth or up to first 3 months of life with heavy proteinuria, hypoalbuminemia, and edema. Later onset, between three months and one year of age, is called **infantile nephrotic syndrome**. Most of these children have a genetic basis for the renal disease and a poor outcome. The precise diagnosis of the glomerular lesion is based on clinical, laboratory, and histological criteria. In a review of 89 Central European and Turkish children (from 80 families) who presented with nephrotic syndrome in the first year of life, 85% of cases during the first 3 months of life could be explained by mutations in one of the following genes:

- 1) **NPHS1** gene encodes nephrin (key component of the podocyte slit diaphragm) and is responsible for the **Finnish-type congenital nephrotic syndrome**.
- 2) **NPHS2** gene encodes podocin (protein that interacts with nephrin) and is responsible for **familial focal segmental glomerulosclerosis**.
- 3) **WT1** gene encodes the transcription tumor suppressor (responsible for kidney and gonad development) and is responsible for the Denys-Drash syndrome.
- 4) **LAMB2** gene encodes laminin beta 2 (a component of the glomerular basement membrane) and is responsible for the Pierson syndrome.

NPHS1 and NPHS2 gene mutations accounted for around 95 percent of cases.

Nongenetic causes are often secondary; possibly curable and include infections like syphilis or toxoplasmosis, and toxins such as mercury exposure.

Congenital Nephrotic Syndrome of Finnish Type (CNF) is most frequent in Finland; initial studies showed an incidence of 1.2 per 10,000 births but with prenatal screening, the incidence has fallen to 0.9 per 10,000 births. CNF is inherited as an **autosomal recessive** trait, with both sexes involved equally. **There are no manifestations of the disease in heterozygous individuals.** It is characterized at birth by a large placenta and subsequently by early onset of symptoms, complete resistance to steroids, and death, usually within the first 2 years of life. **Pathology:** Light microscopy early in the course of the disease shows **mild mesangial hypercellularity and increased mesangial matrix**. No immune deposits on immunofluorescence studies. Tubulointerstitial changes are also prominent with irregular microcystic dilatation of proximal tubules being the most striking feature (neither specific nor in all patients). Later, interstitial fibrosis, lymphocytic and plasma cell infiltration, tubular atrophy, and periglomerular fibrosis develop in parallel with sclerosis of the glomeruli. **Pathogenesis:** Proteinuria in CNF results from an inherited error in the structure of the glomerular capillary filter, the abnormal gene was subsequently localized to the long arm of chromosome 19 in both Finnish and non-Finnish families. The locus for Finnish-type congenital nephrotic syndrome was localized to chromosome 19q12-q13.1. The defective gene in CNF named as NPHS1, encodes for a transmembrane protein **nephrin**. The two most common mutations, Fin-major (nt121delCT) and Fin-minor (R1109X), account for nearly 90 percent

of all affected Finnish patients and are associated with severe early onset of disease. **The nephrin gene consists of 29 exons spanning 26 kb in the chromosomal region 19q13.1.** CNF can be diagnosed prenatally by analyses of the α -fetoprotein levels in the amniotic fluid and maternal serum⁷ and this method has been used especially in high-risk families¹. The disease is progressive during the first 1-2 years of life, and kidney transplantation is the only successful and life-saving treatment for CNF patients⁵. *Loss of the foot processes of the glomerular epithelial cells are the usual findings in electron microscopy*, but no abnormalities are apparent in the glomerular basement membrane (GBM)³. **Clinical features:** Most babies are premature (35-38 weeks), small for gestational age; have large placenta. Fetal distress is common and widely separated cranial sutures due to delayed ossification. Affected babies often have a small nose and low ears; flexion deformities of the hips, knees, and elbows (probably due to large placenta). Edema may be present at birth or appears during the first week of life in 50% of cases. By the age of 3 months almost all babies develop severe nephrotic syndrome with marked ascites; proteinuria is highly selective early in the disease and hematuria is uncommon, reflecting the lack of inflammation in the glomeruli. The urinary protein losses cause profound hypoalbuminemia and severe hypogammaglobulinemia due in part to loss of selectivity as the disease progresses. This results in *failure to thrive and high susceptibility to bacterial infections* (peritonitis, respiratory infections) and to *thromboembolic complications* due to the severity of the nephrotic syndrome. *Hypothyroidism* because of urinary losses of thyroxine-binding proteins is also common. Initial renal function tests are normal. Renal ultrasonography shows enlarged, hyperechogenic kidneys without normal corticomedullary differentiation. End-stage renal disease usually occurs between three and eight years of age. **Treatment:** CNF is always resistant to glucocorticoids and immunosuppressive drugs, since this is not an immunologic disease. Early intravenous albumin supplementation to replace renal losses, nutritional support, vitamin and thyroxin replacement, and rapid management of the complications of infection and thrombosis allow initial stabilization. The diet is provided by tube feeding or by parenteral nutrition. Many times massive proteinuria warrants bilateral nephrectomy before the development of renal failure to prevent such huge protein losses. Combined use of an ACE inhibitor and indomethacin, both of which lower intraglomerular pressure, caused a marked fall in protein excretion and striking improvement in nutritional status and growth in some patients. If nephrectomised, dialysis support is provided until the patient reaches a weight of 8 to 9 kg and then renal transplantation can be considered. Nephrotic syndrome can develop in the transplanted kidney as well most of which have the Fin-major/Fin-major genotype, which is associated with the absence of nephrin and a few patients have circulating antinephrin antibodies. Recurrence of disease is associated with graft loss. The addition of plasmapheresis to oral cyclophosphamide and increased doses of methylprednisolone have shown to improve the remission and graft survival rates of patients with recurrent disease. The management of steroid-resistant nephrotic syndrome is difficult; most patients failing to achieve remission show progressive renal damage. Calcineurin inhibitors (cyclosporine, tacrolimus) are capable of inducing remission in a significant proportion of patients, but at risk of nephrotoxicity. Reduction of proteinuria is also possible, in children, using angiotensin converting enzyme inhibitors and/or angiotensin receptor blockers. **Antenatal diagnosis:** CNF becomes manifest during early fetal life (15-16 weeks gestation) and the initial symptom is fetal proteinuria, which leads to a more than 10-fold increase in the amniotic fluid α -fetoprotein (AFP) levels. A parallel increase in the maternal plasma AFP level is seen. Though not specific, but it may help in the antenatal diagnosis of CNF in high-risk families; termination of the pregnancy might be considered. **CNS AND NPHS2 MUTATIONS:** NPHS2 encodes an integral membrane protein, podocin, which is found exclusively in glomerular podocytes and is the causative gene for an autosomal recessive form of familial FSGS. A few patients with the clinical picture of CNS were found to lack NPHS1 mutations but had either homozygous NPHS2 or recessive NPHS2 mutations. Some patients also have both NPHS1 and NPHS2 mutations, resulting in a triallelic abnormality (homozygous mutations in one gene and a heterozygous mutation in the other) which suggests genetic heterogeneity of congenital nephrotic syndrome and the absence of clear genotype/phenotype correlations.

Focal segmental glomerulosclerosis is a histologic lesion, rather than a disease. It

is either Primary or Idiopathic FSGS, which typically presents with the nephrotic syndrome or Secondary FSGS, which presents with non-nephrotic proteinuria and often renal insufficiency; and is thought to represent *an adaptive response to glomerular hypertrophy or hyperfiltration* (e.g. reduced renal mass) or a *nonspecific pattern of scarring due to a previous injury*. FSGS due to other causes like infections (particularly HIV) toxins (including heroin, interferon, cyclosporine, and pamidronate), genetic abnormalities, and renal atheroembolic disease.

Differentiating primary and secondary FSGS has therapeutic implications.

This case highlights a rare disease which needs a very high index of suspicion keeping in mind the very high morbidity and mortality associated with it and an entirely different treatment plan. Our case also highlights the fact that congenital nephrotic syndrome can also occur if the child is heterozygous for two mutations in the NPHS gene though literature till now states homozygosity at the cause of disease.

REFERENCES

- Hinkes BG, Mucha B, Vlangos CN, et al. Nephrotic syndrome in the first year of life: two thirds of cases are caused by mutations in 4 genes (NPHS1, NPHS2, WT1, and LAMB2). *Pediatrics* 2007; 119:e907.
- Hinkes B, Wiggins RC, Gbadegesin R, et al. Positional cloning uncovers mutations in PLCE1 responsible for a nephrotic syndrome variant that may be reversible. *Nat Genet* 2006; 38:1397.
- HALLMAN N, HJELT L. Congenital nephrotic syndrome. *J Pediatr* 1959; 55:152.
- Hallman N, Norio R, Rapola J. Congenital nephrotic syndrome. *Nephron* 1973; 11:101.
- Levy M, Feingold J. Estimating prevalence in single-gene kidney diseases progressing to renal failure. *Kidney Int* 2000; 58:925.
- Habib R, Bois E. [Heterogeneity of early onset nephrotic syndromes in infants (nephrotic syndrome "in infants"). Anatomical, clinical and genetic study of 37 cases]. *Helv Paediatr Acta* 1973; 28:91.
- Kaplan BS, Bureau MA, Drummond KN. The nephrotic syndrome in the first year of life: is a pathologic classification possible? *J Pediatr* 1974; 85:615.
- Sibley RK, Mahan J, Mauer SM, Vernier RL. A clinicopathologic study of forty-eight infants with nephrotic syndrome. *Kidney Int* 1985; 27:544.
- Huttunen NP, Rapola J, Vilksa J, Hallman N. Renal pathology in congenital nephrotic syndrome of Finnish type: a quantitative light microscopic study on 50 patients. *Int J Pediatr Nephrol* 1980; 1:10.
- Rapola J, Sariola H, Ekblom P. Pathology of fetal congenital nephrosis: immunohistochemical and ultrastructural studies. *Kidney Int* 1984; 25:701.
- Kestilä M, Männikkö M, Holmberg C, et al. Congenital nephrotic syndrome of the Finnish type maps to the long arm of chromosome 19. *Am J Hum Genet* 1994; 54:757.
- Lenkkeri U, Männikkö M, McCready P, et al. Structure of the gene for congenital nephrotic syndrome of the Finnish type (NPHS1) and characterization of mutations. *Am J Hum Genet* 1999; 64:51.
- Savage JM, Jefferson JA, Maxwell AP, et al. Improved prognosis for congenital nephrotic syndrome of the Finnish type in Irish families. *Arch Dis Child* 1999; 80:466.
- Kestilä M, Lenkkeri U, Männikkö M, et al. Positionally cloned gene for a novel glomerular protein—nephrin—is mutated in congenital nephrotic syndrome. *Mol Cell* 1998; 1:575.
- Pollak MR. Inherited podocytopathies: FSGS and nephrotic syndrome from a genetic viewpoint. *J Am Soc Nephrol* 2002; 13:3016.
- Lahdenperä J, Kilpeläinen P, Liu XL, et al. Clustering-induced tyrosine phosphorylation of nephrin by Src family kinases. *Kidney Int* 2003; 64:404.
- Ruotsalainen V, Ljungberg P, Wartiovaara J, et al. Nephrin is specifically located at the slit diaphragm of glomerular podocytes. *Proc Natl Acad Sci U S A* 1999; 96:7962.
- Tryggvason K. Unraveling the mechanisms of glomerular ultrafiltration: nephrin, a key component of the slit diaphragm. *J Am Soc Nephrol* 1999; 10:2440.
- Rantanen M, Palmén T, Pääri A, et al. Nephrin TRAP mice lack slit diaphragms and show fibrotic glomeruli and cystic tubular lesions. *J Am Soc Nephrol* 2002; 13:1586.
- Patrakka J, Kestilä M, Wartiovaara J, et al. Congenital nephrotic syndrome (NPHS1): features resulting from different mutations in Finnish patients. *Kidney Int* 2000; 58:972.
- Niaudet P. Genetic forms of nephrotic syndrome. *Pediatr Nephrol* 2004; 19:1313.
- Shih NY, Li J, Karpitskii V, et al. Congenital nephrotic syndrome in mice lacking CD2-associated protein. *Science* 1999; 286:312.
- Kitamura A, Tsukaguchi H, Hiramoto R, et al. A familial childhood-onset relapsing nephrotic syndrome. *Kidney Int* 2007; 71:946.
- Koziell A, Grech V, Hussain S, et al. Genotype/phenotype correlations of NPHS1 and NPHS2 mutations in nephrotic syndrome advocate a functional inter-relationship in glomerular filtration. *Hum Mol Genet* 2002; 11:379.
- Schultheiss M, Ruf RG, Mucha BE, et al. No evidence for genotype/phenotype correlation in NPHS1 and NPHS2 mutations. *Pediatr Nephrol* 2004; 19:1340.
- Wong W, Morris MC, Kara T. Congenital nephrotic syndrome with prolonged renal survival without renal replacement therapy. *Pediatr Nephrol* 2013; 28:2313.
- Ljungberg P, Holmberg C, Jalanko H. Infections in infants with congenital nephrosis of the Finnish type. *Pediatr Nephrol* 1997; 11:148.
- Pomeranz A, Wolach B, Bernheim J, et al. Successful treatment of Finnish congenital nephrotic syndrome with captopril and indomethacin. *J Pediatr* 1995; 126:140.
- Heaton PA, Smales O, Wong W. Congenital nephrotic syndrome responsive to captopril and indomethacin. *Arch Dis Child* 1999; 81:174.