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The pediatric nephrotic syndrome spectrum: Clinical homogeneity and molecular heterogeneity

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Abstract

Idiopathic nephrotic syndrome is the most common glomerular disorder of childhood. Recurrence of nephrotic syndrome immediately following renal transplantation is rapid, results in a high rate of graft loss, and represents the most severe form of nephrotic syndrome. This review discusses the molecular heterogeneity of pediatric nephrotic syndrome across the spectrum of disease activity. A schema is offered for a molecular approach to pediatric nephrotic syndrome, including immune-mediated and structural/genetic factors.

Keywords

nephrotic syndrome; focal segmental glomerulosclerosis; kidney transplantation; recurrence

Abbreviations

CMV, cytomegalovirus; EM, electron microscopic; ESRD, end-stage renal disease; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; IL-2, interleukin-2; LM, light microscopic; NF- κ B, nuclear factor kappa B; NON-NS, non-nephrotic syndrome; NS, nephrotic syndrome; R-NS, recurrence of nephrotic syndrome; SRNS, steroid resistant nephrotic syndrome; SSNS, steroid sensitive nephrotic syndrome; TGF β , transforming growth factor beta; TNF α , tumor necrosis factor alpha; VEGF, vascular endothelial growth factor

R-NS after transplantation is an important problem in adult and pediatric transplantation. R-NS may be considered the most severe form of NS in native kidneys (Fig. 1). Therefore, an understanding of the mechanisms underlying R-NS is best served by examining the molecular mechanisms of NS. The main theme of this review is that the primary pediatric NS spectrum (including R-NS) is a clinically homogeneous syndrome, that is molecularly heterogeneous with as yet no group of biomarker-based classification schema.

Pediatric nephrotic syndrome

Idiopathic NS is the most common glomerular disorder of childhood. It is distinct from secondary causes of NS, such as obstructive uropathy, chronic allograft nephropathy, lupus nephritis, IgA nephropathy, and viral infections such as hepatitis and HIV. Renal biopsy pathologic changes in NS, including minimal change disease and FSGS have remained the gold standard diagnostic classification for decades. However, the prognosis of NS in children correlates with the spectrum of responsiveness to steroid therapy, from SSNS to SRNS. SRNS is the most common acquired cause of ESRD in children. It accounts for approximately 15%

of pediatric and 5% of adult cases of ESRD in North America (1,2). Recent reports indicate that the incidence of SRNS is increasing, and may now represent 23% of all pediatric NS (3, 4). Moreover, the incidence of steroid resistance and poor outcome may be higher in African-American children, although the risk of post-transplant recurrence may be lower in this population (5,6).

Recurrence of SRNS immediately following renal transplantation is rapid, results in a high rate of graft loss, and represents the most severe form of NS. R-NS occurs in up to 50% of cases and is associated with a 50% risk of renal allograft loss (7–10). The median time to recurrence is 14 days after transplantation (8) but may occur anytime post-transplant, ranging from hours to months. The nature and timing of early recurrence suggests a role for a systemic abnormality or circulating factor present at the time of transplantation in this severe subgroup of primary pediatric NS.

Clinical manifestations and pathophysiology

The heterogeneity of the clinical course of NS and R-NS is in stark contrast to the homogeneity of initial clinical manifestations and pathophysiology. The primary pathophysiologic event in NS has been shown to be the loss of selectivity for albumin in the GBM. The increased permeability to albumin in the GBM is believed to be due to a combination of increase in the size of the functional pores between the cords of type IV collagen, and loss of anionic charge normally present in the form of heparan sulfate proteoglycans. The resulting massive loss of albumin into the urine results in hypoalbuminemia, which in turn causes effective circulating fluid volume depletion and decreased intravascular oncotic pressure. Compensatory physiologic mechanisms result in sodium retention (renin-angiotensinaldosterone) and free water retention. The combination of decreased intravascular oncotic pressure and sodium/water retention results in dependent edema that is most noticeable in the supra-orbital region, abdomen, inguinal/scrotal region, and lower limbs. Hyperlipidemia in NS is believed to be the result of loss of lipoprotein lipase into the urine. Non-albumin proteins lost in the urine include immunoglobulins, clotting factors, and several important binding proteins in the plasma, including several hormonal binding proteins. As a result of loss of immunoglobulins NS patients are prone to infection even before immunosuppressive therapy is initiated, and severe ascites may be complicated by spontaneous bacterial peritonitis. Thrombotic events have been reported in the portal vein, sagittal sinus, and various limb vessels. Disorders of thyroid and parathyroid function are occasionally seen. Up to 25% of pediatric NS patients may also demonstrate glomerular hematuria and red blood cell casts in the spun urine sediment.

By definition NS includes nephrotic-range proteinuria (age-dependent), hypoalbuminemia, edema and hyperlipidemia. While the severity of these manifestations may vary (some patients have severe edema while others have very mild edema), their presence provides no meaningful prognostic information. Pediatric patients who present with new-onset NS and no identifiable cause such as systemic lupus erythematosus or IgA nephropathy are routinely administered an 8–12-wk course of high dose daily oral steroid therapy, which is as much a diagnostic maneuver as a treatment. Patients who experience disease remission within 4–8 wk of initiating steroid therapy are weaned off steroids and do not undergo further diagnostic evaluation unless future relapses occur during a steroid taper or are unresponsive to steroid therapy. Of note, many children with frequently relapsing SSNS will ultimately transform to SRNS. The indications for a renal biopsy in a patient with NS are either steroid-dependence (relapse while receiving steroid therapy at any dose or within 2 wk of completing a steroid taper) or steroid resistance.

Histopathologic changes observed in primary NS renal biopsies are most evident in LM and EM studies. LM findings in minimal change are generally normal, while in FSGS include focal and segmental glomerular sclerosis and scarring associated with tubular scarring and interstitial

fibrosis. EM evaluation of ultrastructural changes often reveals effacement of glomerular epithelial foot processes in minimal change specimens or FSGS. Several histopathologic variants of FSGS have been described, including tip, collapsing, cellular, classical and perihilar variants (11–13). However, none of these variants have been proven to be of prognostic value, particularly in the pediatric population.

Numerous animal models of NS exist with histopathological changes consistent with FSGS, including those induced by viral infection or specific medications. Other models demonstrate FSGS associated with altered glomerular hemodynamics secondary to hyperfiltration and nephronopenia (14), and chronic cyclosporine therapy (15). While these models provide valuable insight into the pathogenesis of FSGS as a common end-stage glomerular lesion, none are accurate representations of the primary form of SRNS that constitutes up to 15% of cases of ESRD in children. While these models are crucial to the study of FSGS that is secondary to known disturbances, such as HIV nephropathy, IV drug abuse, and congenital or acquired nephronopenia, they are unlikely to help elucidate the etiology of primary NS in children. While these models are crucial to the study of FSGS that is secondary to known disturbances, such as HIV nephropathy, IV drug abuse, and congenital or acquired nephronopenia, they are unlikely to help elucidate the etiology of primary NS in children.

Biomarkers for pediatric NS and R-NS

The focal nature of FSGS impedes the prognostic utility of renal biopsy analysis in pediatric NS. A routine renal biopsy will yield approximately 8–20 glomeruli, out of a total of 1 million glomeruli normally present in a kidney. If the sample is obtained from an area of kidney that does not contain sclerosis, a patient with FSGS will be diagnosed with minimal change disease. As well, renal biopsies are performed only for children with SRNS and steroid dependence. Children with SSNS are treated with steroid therapy until either (1) the relapses stop occurring, or (2) the disease transforms to frequently relapsing NS or SRNS, in which case a renal biopsy would then be performed. Renal biopsy is therefore an inaccurate test obtained from a skewed population, and cannot provide an appropriate primary NS control group without subjecting SSNS children to a clinically unnecessary and invasive procedure.

Although loss of glomerular selectivity for albumin is common to all types of NS, many different and seemingly unrelated genomic and molecular markers correlate with NS disease course, again supporting the molecularly heterogeneous nature of the NS group of disorders. These markers can be divided into two categories: *immune-related* and *structural*.

Immune-related biomarkers in pediatric NS and R-NS

Evidence supporting an immune mechanism in NS dates back 40 years, when it was shown that immunosuppressive therapy could induce remission of many cases of NS. Several studies have demonstrated altered T cell subsets in NS, albeit with conflicting results between studies (16–20). The high incidence and rapid rate of recurrence of SRNS following renal transplantation supports the concept of a pathogenic circulating factor in this subgroup of patients. Both plasmapheresis (21,22) and protein A adsorption (23) have been used to isolate and study the characteristics of a plasma factor or group of factors, which may mediate proteinuria. Many known circulating substances have been implicated in NS including IL-2 (24–26), IL-2 receptor (25), IL-4 (26,27), IL-12 (28,29), IL-13 (17), IL-15 (28), IL-18 (30, 31), interferon-gamma (26,29), TGF β (32,33), VEGF (34), vascular permeability factor (32), NF- κ B (35,36), and TNF α (37–39). Because TNF α activates NF- κ B and angiotensinogen (40), and because steroid-induced immunosuppression is critically dependent upon inhibition of NF- κ B, our group measured intra-graft gene expression of the NF- κ B p65 subunit as well as the natural inhibitor of NF- κ B (I κ B α), and angiotensinogen in a cohort of pediatric patients with R-NS (35). We showed that the NF- κ B : I κ B α ratio is higher in R-NS vs. NON-NS (14.0

± 2.3 vs. 9.5 ± 1.5 , respectively), and is significantly affected by diagnosis (NON-NS vs. R-NS, $p = 0.05$), and rejection status ($p = 0.01$), but not by prednisone dose, cyclosporine dose, induction therapy, CMV infection, serum creatinine level, or post-transplant day. We also demonstrated significantly increased levels of intra-graft angiotensinogen gene expression in R-NS vs. NON-NS (median levels 16.7 ag/fg [attogram/femtogram] in R-NS vs. 6.5 ag/fg in NON-NS, $p = 0.009$). Studies in adults have demonstrated increased NF- κ B DNA binding activity and decreased I κ B α mRNA expression in NS patients in relapse vs. remission (36).

Structural biomarkers in pediatric NS and R-NS

In contrast to circulating substances, structural abnormalities in one or more key components of the glomerular basement membrane cause nephrotic-range proteinuria, NS, and in some instances, familial NS. Family studies have resulted in the mapping of a gene for autosomal dominant FSGS to human chromosome 19q13 (locus FSGS-1) in a large family from Oklahoma (41). Genotyping family members at markers on chromosome 19q13 narrowed the candidate interval to a 3.5-Mb region flanked by *D19S609* and *D19S417*. In one additional small family from California, the disease segregated with chromosome 19q13.1 marker alleles. Mutations in the gene encoding α -actinin-4 (*ACTN4*) on chromosome 19q13.1, an actin-filament crosslinking protein, were discovered as the cause of FSGS in three families with an autosomal dominant form of FSGS (42). Based on actin-binding experiments, it was shown that these mutations result in altered regulation of the actin cytoskeleton of glomerular podocytes, the epithelial cells that play a key role in the glomerular basement membrane. A second locus for dominant FSGS has been identified on chromosome 11q22–24 in one family (43) and a recessive locus has been reported on chromosome 1q (44).

Congenital NS of the Finnish type has been shown to be the result of defects in both alleles of the *NPHS1* gene, which encodes nephrin, a transmembrane protein located at the glomerular epithelial cell slit diaphragm (45). Recently, our group has shown that a mutation in the *NPHS2* gene encoding the glomerular epithelial cell component, podocin, is the cause of FSGS in a subgroup of affected families. *NPHS2* mutations in 30 families with autosomal recessive SRNS, and in 91 individuals with primary NS revealed that nine of the 30 families were found to have *NPHS2* mutations that were the likely cause of recessively inherited NS. For six of these nine families, affected individuals were compound heterozygotes for a non-conservative R229Q amino acid substitution in the podocin protein (46).

Molecular classification of disease spectra

Many diseases that manifest as a spectrum of related disorders have been the subjects of molecular classification studies, most commonly by high-throughput RNA analysis, and more recently by proteomic methods. A well-cited example of RNA expression profiling is the report on distinct subtypes of B-cell lymphoma (47). A benefit of utilizing mRNA (or cDNA) for expression profiling is that the technology has improved to the point that most probes and probe sets are highly gene-specific, and the number of genes on a single chip is increasing dramatically. There are however many disadvantages to using high-throughput RNA hybridization arrays for disease profiling, including the high cost per sample, the unreliability of measurements for genes expressed at relatively low-levels, and the general lack of correlation with protein expression largely because of differential RNA splicing and post-translational modification. High-throughput proteomic technology is now reaching the point where sophisticated high-throughput studies are feasible and cost-effective, as well as biologically informative and relevant. In this context, the use of urine is based on precedent in the literature. Urine mRNA expression has been shown to be a valuable tool for non-invasive diagnosis of acute renal allograft rejection (48). A similar study demonstrated the utility of urine proteomics for the diagnosis of renal allograft rejection (49).

Summary

In summary, R-NS is a severe form of the primary pediatric NS spectrum, and NS is an important cause of morbidity in the pediatric population. The multitude of molecular candidates suggests that primary pediatric NS and R-NS are clinically homogeneous syndromes, that are molecularly heterogeneous with as yet no single specific biomarker or group of biomarkers. Table 1 shows one of many possible schemata for approaching this heterogeneous group of disorders at the molecular level. The time is ripe to perform molecular studies that can provide more detailed, accurate, and informative diagnostic and prognostic information for clinicians and investigators.

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Fig. 1.

The spectrum of pediatric nephrotic syndrome is shown, including SSNS, SRNS, ESRD and transplantation, and several outcomes following transplantation, including recurrence following transplantation (R-NS). Note that some arrows are bidirectional, indicating that patients can ‘transform’ between SSNS and SRNS depending on disease course and therapeutic response. As well, those who achieve remission of R-NS may experience another episode of R-NS with the same allograft or a subsequent allograft. Those who do not experience R-NS are still prone to the same causes of allograft loss as all other renal transplant recipients (e.g. chronic allograft nephropathy).

Table 1

Schema for a molecular approach to pediatric NS and R-NS. This table represents a partial list of molecular entities implicated in the pathogenesis of NS

Category	Examples (see text for details)
Immune-Mediated	Immunoabsorption/protein A 'circulating' permeability factors Interleukins: IL-2, IL-2R, IL-4, IL-12, IL-13, IL-15 and IL-18 Interferon- γ (IFN γ) Transforming growth factor β (TGF β) Tumor necrosis factor alpha (TNF α) Vascular endothelial growth factor (VEGF) Vascular permeability factor Nuclear factor kappa B (NF- κ B), I κ B Angiotensinogen
Structural/genetic	α -Actinin-4 (<i>ACTN4</i>) Nephlin (<i>NPHS1</i>) Podocin (<i>NPHS2</i>)