ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Paediatric Nephrotic Syndrome: A Review.

Vanmathi SM*, Sujitha P J and Sambathkumar R.

Department of Pharmacy Practice, J.K.K Nattraja college of Pharmacy, Komarapalayam-638183, Tamil Nadu, India.

ABSTRACT

Nephrotic syndrome (NS) is a common pediatric kidney disease and is defined as massive proteinuria, hypoalbuminemia, and edema. Dysfunction of the glomerular filtration barrier, which is made up of endothelial cells, glomerular basement membrane, and visceral epithelial cells known as podocytes, is evident in children with NS. While most children have steroid-sensitive nephrotic syndrome (SSNS), only 20% have steroid-resistant nephrotic syndrome (SRNS) and are at risk for progressive kidney dysfunction. More than 30 proteins regulating the function of the glomerular filtration barrier has been associated with SRNS including podocyte slit diaphragm proteins, podocyte actin cytoskeletal proteins, mitochondrial proteins, adhesion and glomerular basement membrane proteins, transcription factors, and others. Idiopathic nephrotic syndrome (INS) in children is characterized by massive proteinuria and hypoalbuminemia. Minimal change nephrotic syndrome (MCNS) is the most common form of INS in children. The pathogenesis of MCNS still remains unclear, however, several hypotheses have been recently proposed. For several decades, MCNS has been considered a T-cell disorder which causes the impairment of the glomerular filtration barrier with the release of different circulating factors. Increased levels of several cytokines are also suggested. This review summarizes the pathological characteristics of these conditions, and also delves into various genetic defects that have been described as the cause of this nephrotic syndrome in paediatrics.

Keywords: nephrotic syndrome, proteinemia, minimal change disease, pathogenesis.

https://doi.org/10.33887/rjpbcs/2019.10.6.9

Corresponding author

ISSN: 0975-8585

INTRODUCTION

The kidney is the main organ of filtration in the body, and the daily protein loss is only a small portion of the total protein ingested. Nephrotic syndrome (NS) is characterized by heavy proteinuria that exceeds 1.66 g/1.73 m2/day in children, edema, Hypoalbuminemia, and hyperlipidemia.1 Although the causes of NS are many and diverse, it is a frequent cause of renal disease in children with an annual incidence of about two to seven children per 100,000.1 The International Study of Kidney Disease in Children lists minimal change disease (MCD) as the commonest cause of primary NS in children affecting 77% of the children followed by focal segmental glomerulosclerosis (FSGS) at about 8% followed by membrano proliferative glomerulonephritis (MPGN) and membranous glomerulonephritis.2 Minimal change disease (MCD) is the most common histological variant of nephrotic syndrome and accounts for approximately 80% of cases in children based on historical data from 1967 to 1976.3 Focal segmental glomerulosclerosis (FSGS) is less common but can be progressive with poor long-term outcomes. Children with SSNS generally have a favorable outcome, and the results of older studies suggested they achieve long-term remission during teenage years. However, recent data suggest that over 30 % of SSNS children relapse in adulthood. More than 60 % of children with SRNS who fail to achieve remission with pharmacological intervention will progress to end-stage renal disease. There are also differences in mortality rates according to the initial response to Gene therapy: 2.7 % in the INS population overall, 18.5 % in children with SRNS, 6.3 % in children with early relapse following initial remission and 0.4 % in children without early relapse. Over the past 15 years genetic discoveries have vastly improved our understanding of the molecular basis of NS. The PodoNet consortium has recently reported data from a heterogeneous population of 1655 children with SRNS with a median follow-up time of 3.7 years. 4.

Etiology

The etiology of most cases of SSNS is unknown and are therefore given the label “idiopathic or primary SSNS”. The definitive reason why some patients respond to corticosteroids and others do not escapes explanation, but proposed mechanisms underlying the pathogenesis of SSNS have sought to clarify this variability in pattern of response. Shalhoub and colleagues in the year 1970s proposed that SSNS is the result of a primary T-cell dysfunction based on the evidence that nephrotic syndrome responds to immunosuppressive agents like corticosteroids and calcineurin inhibitors which modulate T-cell function there are reported cases of patients achieving remission following diseases, such as measles or malaria that are known to suppress cell-mediated immunity, and there are patients who develop nephrotic syndrome as part of a paraneoplastic process in malignancies known to affect T-cell function such as Hodgkins lymphoma. Subsequent studies have explored changes in T-cell surface expression, function, and cytokine release in the setting of nephrotic syndrome, however experimental recapitulation of these findings in multiple studies have been lacking.[5-7]

Causes of nephrotic syndrome in children.

Genetic

- Congenital NS of Finish type
- Diffuse mesangial sclerosis (DMS)
- Isolated DMS
- Part of Denys–Drash syndrome
- Epidermolysisbullosa associated
- Steroid-resistant nephrotic syndrome
- Familial focal segmental glomerulosclerosis (FSGS)

Infections

- Congenital infections including syphilis, toxoplasmosis, and HIV
- Cytomegalovirus
- HIV-associated nephropathy

Idiopathic

- Minimal change nephropathy
- Focal segmental glomerulosclerosis
- Diffuse mesangialhypercellularity
- Membranous glomerulonephritis
- Membranoproliferative GN (MPGN) (NS may predominate or with nephritic syndrome)

Others

- Lupus nephropathy
- IgA nephropathy
- Drugs
- Malignancies
- Hemolytic uremic syndrome (HUS)

Pathophysiology of NS

The primary defect in NS is loss of proteins in the kidney. Although lack of tubular reabsorption could lead to proteinuria, NS range proteinuria usually implies permeability defects in the glomerular membrane that results in this excessive protein loss. This leads to albuminuria and hence the associated hypoalbuminemia and edema, the two main manifestations of NS. The hyperlipidemia is usually due to the increased lipoprotein synthesis induced by the hypoalbuminemia, and this may lead to increased platelet aggregation and thrombosis, one of the complications of NS. The loss of other proteins, minerals, and vitamins with the proteinuria may also predispose to malnutrition and infections. The most dramatic advances for understanding the pathophysiology of NS has occurred in the area of podocyte biology and the structure of the slit diaphragm.[8] The glomerular filtration barrier consists of the fenestrated capillary endothelium, the extracellular basement membrane, and the intercalated podocyte foot processes. NS is associated with the biopsy finding of effacement of podocyte foot processes. Effacement is characterized by flattening of the podocyte, retraction of foot processes, and sometimes microvillous transformation.[9]It has also been understood that MCNS and FSGS can be classified as podocytopathies, in which disruption of slit diaphragm and normal podocyte function can lead to proteinuria and glomerular disease.[10]

Genetic factors in outcome of NS

One of the new factors that may predict response to therapy and renal outcomes are genetic variants of NS. Genetic mutations are most likely to be identified in congenital nephrotic syndrome (CNS). Mutations in NPHS1, NPHS2, LAMB2, and WT-1 were identified in two-thirds of a largely European cohort of 89 infants with NS under the age of 1. The overall average age of ESRD (End Stage Renal Disease) was 5.6 years. While the numbers were small and many outcomes were not known, patients with NPHS1 mutations had ESRD at an average age of 4.6 years, whereas those with NPHS2 mutations had ESRD at an average age of 7.4 years.[11] It is possible these differences could be explained by differences in clinical course and management of congenital NS (e.g., nephrectomies), rather than the genetic basis of disease. However, it suggests that addi-tional studies should address whether specific genetic mutations correlate with outcomes in early onset NS. There are well over 40 genetic mutations associated with FSGS, and new mutations continue to be identified.[12] A single-gene mutation may be identified in up to 29% of patients with SRNS onset prior to age 25.[13] Patients with genetic mutations are less likely to respond to immunosuppressant therapy and more likely to develop ESRD. One of the largest studies examined renal outcomes of at 10-year follow-up of 231 children in a European cohort with SRNS. For those presenting after 3 months of age, 58% children with SRNS associated with genetic mutations had progressed to ESRD, versus 29% with SRNS and no genetic mutation identified. Recently, genetic variants in *APOL1* were identified as risk factors for renal disease in people of African descent. Carrying two copies of *APOL1* coding vari-ants (G1 and G2) is a risk factor for hypertensive nephropathy, lupus nephropathy, FSGS, and HIV nephropathy.[14]

ISSN: 0975-8585

Table 1 Genesinvoled in Nephrotic syndrome

S.No	Genes	Location	Protein	Significant clinical association
1.	NPHS1	19q13.12	Nephrin	CNS Finnish type
2.	NPHS2	1q25.2	Podocin	Steroid-resistant NS; rapidly progressive renal disease; FSGS
3.	WT1 (NPHS4)	11p13	Wilms' tumor 1	Denys–Drash syndrome; nephrotic syndrome–FSGS; Frasier syndrome
4.	SMARCAL1	2q35	SW1/SNF related	Schimkeimmunoosseous dysplasia
5.	PLCE1 (NPHS3)	10q23.33	Phospholipase CE1	DMS, FSGS
6.	PTPRO	12p12.3	Protein tyrosine phosphatase, receptor-type O	Steroid-resistant NS
7.	LAMB2	3p21.31	Laminin, beta-2	CNS with ocular abnormalities; Pierson syndrome
8.	INF2 (FSGS 5)	14q32.33	Inverted formin 2	FSGS
9.	COQ6 FSGS, DMS	14q24.3	Coenzyme Q10 def, primary 6	Progressive NS in infancy with sensorineural deafness;
10.	MYO1E (FSGS6)	15q21	Myosin 1E	FSGS (AR)
11.	TRPC6 (FSGS2)	11q22.1	Transient receptor potential cation channel, subfamily C, member 6	FSGS (AD)
12.	COQ2	4q21.23	Coenzyme Q10 deficiency-1	Steroid-resistant NS
13.	LMX1B	9q33.3	LIM homeobox transcription factor 1, beta	Nail–patella syndrome
14.	ADCK4 (NPHS9)	19q13.2	AARF domain-containing kinase 4	NS (AR)
15.	PDSS2	6q21	Prenyldiphosphatesynthese, subunit 2	NS
16.	ACTN4 (FSGS1)	19q13.2	Alpha-actinin-4	FSGS
17.	CD2AP (FSGS3)	6p12.3	CD2-associated protein	FSGS
18.	MYH9	22q13.1	Non-muscle myosin IIA heavy chain	FSGS, collapsing glomerulopathy

Edema nephrotic syndrome

Edema is an essential clinical feature of the diagnosis of nephrotic syndrome (NS) of various etiologies. It is defined as a palpable swelling resulting from an accumulation of fluid in the interstitial fluid compartment. Massive generalized edema (anasarca) is common, especially in children with primary minimal change disease (MCD) and serves as the main clinical justification for hospital admission for "diuretic management." In such children, the selective loss of large amounts of albumin in the urine leads to hypoalbuminemia and decreased plasma oncotic pressure favoring fluid sequestration in the interstitial fluid compartment, and secondarily triggers renal Na+ and fluid retention so as to preserve intravascular volume and blood pressure, hence preventing an "underfill" state. In contrast to MCD, in NS associated with glomerulonephritis the magnitude of the proteinuria is variable and reduction in GFR is common.[15]

Factors That Protect Against edema Formation in NS

Normally there is a small net pressure gradient favoring net filtration across capillaries, it might be expected that only a minor change in these hemodynamic forces would lead to edema. However, experimental and clinical observations indicate that there must be at least a 15 mmHg increase in the net pressure gradient favoring filtration before edema can be detected. With lesser reduction of this gradient, edema is unlikely to occur because of three compensatory factors.[16,17] First, experimental evidence indicates that there is increased lymphatic flow which, by bulk flow, will remove albumin as well, and help remove some of the excess filtrate[18,19]. Second, fluid entry into the interstitium will eventually raise the interstitial hydraulic pressure, thereby oppose filtration and interstitial fluid accumulation.[17] Third, fluid accumulation in the interstitium

simultaneously reduces interstitial oncotic pressure in subcutaneous tissue which in humans it is normally 12–15 mmHg.[20] Thus, a gradual fall in plasma oncotic pressure in NS is associated with a parallel decline in interstitial oncotic pressure and rise in interstitial hydraulic pressure,[16] which minimizes the change in the transcapillary pressure gradients favoring net fluid movement out of the vascular space and results in relative preservation of plasma volume. **T**he role of hypoalbuminemia in children with nephrotic edema explains, with the exception of marked hypoalbuminemia (<2.0 g/dL) and plasma oncotic pressures below 8–10 mmHg, several clinical and experimental observations call into question the central role of hypoalbuminemia in the pathogenesis of nephrotic edema.[21]

Management of Nephrotic Syndrome

Before reviewing the management of edema in children with NS it is worth noting the change in the incidence of known clinical complications of NS that may relate to edema or its improper medical management. In a recent study involving hospital discharges of 4,701 children admitted with NS, Another study found that the frequency of infectious and thromboembolic complications has not changed much over the past 10 years; however, the incidence of AKI (Acute kidney Injury) had increased from 3.3 to 8.5% (158%) over the period of 2001 and 2009.[22] The increasing use of nephrotoxic medications such as calcineurin inhibitors and angiotensin converting enzyme/angiotensin receptor blockers to co-manage steroid dependent and steroid resistant NS may be partly responsible for this trend. However, aggressive diuresis in children not recognized as having intravascular volume depletion (underfilling) may enable progression from incipient AKI to established AKI. Furthermore, prevention of AKI is of great importance because it may be a precursor to future development of chronic renal injury and hypertension. Inappropriate diuresis may also promote a thrombotic tendency in this disorder.[23-26]Consequently, children with "underfill" physiology may benefit first by circulatory volume expansion using salt-poor albumin infusions, and delayed start of diuretics until after restoration of tissue perfusion is achieved.

Pharmacological Treatment

Table 2 Management of Edema in children

Diuretic class, name	Bioavailability % PO/IV ratio	Onset of action (min) PO/IV	Duration of action (h)	Dosing
Loop diuretics				
Furosemide	60	40/5	6	Neonates: p.o. 1–4 mg/kg/dose, 12 × / day iv/im 1–2 mg/kg/dose q 12–24h
Bumetanide	85	40/5	4	Children: p.o./iv/im 1–2 mg/kg/dose q 6–12 h
Torsemide, Ethacrynic acid				<6 months: p.o./iv/im 0.05–0.05 mg q 24 h >6 months: p.o./iv/im 0.015 mg/kg q 24 h; max. 0.1 mg/kg/dose
Thiazide diuretics				
Chlorothiazide	11-20	120	24	<6 months: p.o. 20–40 mg/kg/day divided bid iv 2–8 mg/kg/day divided bid
Hydrochlorothiazide	60-75	120	12-24	>6 months: p.o. 20 mg/kg/day divided bid iv 4 mg/ kg/day
Thiazide-like				
Metolazone	40-60	60	24	Children: 0.2–0.4 mg/kg/day divided q 12–24 h

Albumin infusion In hospitalized children with nephrotic edema, excessive fluid can usually be removed, relatively safely, without exacerbating volume depletion. This is often accomplished through the combined administration of salt-poor, or, 25% albumin (SPA) to facilitate reabsorption of IS fluid, thereby supporting plasma volume and diuretics to enhance fluid removal. The more available 5% albumin solution can increase blood volume but does not raise oncotic pressure, while it delivers fivefold higher Na+ for each gram of albumin infused. By expanding plasma volume, albumin infusion suppresses vasopressin release induced by

hypovolemia, thereby increasing water diuresis and improvement in hyponatremia. Albumin infusion is associated with more profound diuresis, at least in a subpopulation of pediatric patients with NS,[27-30] particularly those with reduced effective arterial blood volume. By contrast, concurrent use of diuretics and salt-poor albumin or diuretic monotherapy is often utilized to manage edema in the inpatient setting. Many children with NS respond well to loop diuretics, although there is generally lesser natriuresis than when such diuretics are utilized to manage edema associated with other medical disorders.[31] Experimental studies in drug-induced NS suggest that the loop of Henle may be relatively resistant to loop diuretics.[32]

In children who do not respond adequately to loop diuretics, it is advisable to add a thiazide type diuretic in order to achieve diuretic synergy by way of sequential nephron blockade. Chlorothiazide can be given orally or intravenously and is particularly useful in small sized children or if gastrointestinal absorption is compromised. For oral use in children over 5 years old, the author prefers short-term use of metolazone (Zaroxolyn), a long acting thiazide-likediuretic, which is secreted in the proximal tubule and has a plasma half-life of 36-hours; it is given at a dosage of 2.5–5.0 mg once daily. Like most loop diuretics, metolazone is also highly protein bound and, therefore, it is not dependent on normal GFR for it to be effective. When this is combined with bumetanide and SPA, a brisk diuresis is usually achieved. Although ENacchannel activation has been implicated in Na+ retention in NS of diverse etiologies, the efficacy of blocking this channel by amiloride is believed to be low because of the relatively small amount of Na+ arriving at the DCT. However, amiloride and other potassium sparing diuretics, such as spironolactone (1.25 mg/kg/dose), may be utilized in conjunction with loop diuretics.[33]

Non-Pharmacological treatment

Apart from managing the underlying condition leading to NS, established guidelines suggested that [34-37], due to sodium, fluid retention is the fundamental feature of all causes of NS and because treatment regimens that include corticosteroids tend to enhance this effect, all children presenting with edema are counseled on dietary Na+ restriction (35 mg Na+/kg/day, or approximately1.5 mEq/kg/day) and are monitored for clinical signs of hypovolemia.[38] Fluid restriction is usually self-limited in children who adhere well to Na+ restriction, and it is not recommended in children managed in the outpatient setting. Attention to nutrition is very important particularly in conditions associated with massive proteinuria, such as Finnish type (caused by mutation in NPHS1 gene and is inherited in autosomal recessive manner) NS. Given the $T_{1/2}$ of albumin of 21 days, when provided with adequate calories and amino acids, the liver can produce 200 mg albumin/kg/day to replace albumin catabolism or urinary loss. This normal synthetic function can double when the oncotic pressure in hepatic sinusoids falls as in the setting of NS. Provision of supplemental calories, egg white protein, and nutritional supplements, such as Boost or Pediassure, may be helpful if clinically indicated. Diuretic therapy should be temporarily discontinued if there is an unexplained decrease in urine output, elevation in serum creatinine or clinical manifestations of hypovolemia (e.g., weakness, orthostatic hypotension, and/or cool extremities) [39]

Recent aspects and area to be researched

The mainstay of current therapy is immunosuppression, which is appropriate for the immune-mediated group of diseases, but there is very limited evidence of efficacy in monogenic disease. There are studies that support a direct effect of some immunosuppressive drugs on the podocyte, [40-42] though the majority of clinical evidence points to efficacy being achieved via effects on the immune system. Some newer therapies have been proposed on the basis of direct targeting of either the immune system or podocytesignalling pathways. The most prominent of these are the use of anti-CD20 monoclonal antibodies[43], which deplete B cells, and anti-B7-1 monoclonal antibody therapy[44]. The latter has been proposed following the observation that in certain experimental and human glomerular diseases the T-cell co-stimulatory molecule B7-1 has been noted to be upregulated on podocytes. This can be targeted by the drug abatacept and is the subject of current trials in larger numbers of patients. NS is a complex disorder and more research needs to beperformed to ensure informedmanagement decisions aremade.Infection should be treated promptly with broad-spectrum antibioticsin the nephrotic child.[45]

CONCLUSION

Underlying renal pathology, genetic factors, likely modulate response to treatment and progression of ESKD. Many of the long-term complications of childhood SSNS can be attributed to immunosuppressant therapy. The pathology of podocytopathies have some unique and some overlapping features and are frequently associated with specific genetic mutations.It is likely that genetic and environmental risk factors play a substantial role in explaining these ethnic differences. As genetic testing becomes more prevalent and affordable, we expect rapid advances in our understanding of mechanisms of proteinuria creating an opportunity to personalize treatment in the future with a "precision medicine" approach for both adults and children with nephrotic syndrome.

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