Seminar

Nephrotic syndrome in childhood

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Childhood nephrotic syndromes are most commonly caused by one of two idiopathic diseases: minimal-change nephrotic syndrome (MCNS) and focal segmental glomerulosclerosis (FSGS). A third distinct type, membranous nephropathy, is rare in children. Other causes of isolated nephrotic syndrome can be subdivided into two major categories: rare genetic disorders, and secondary diseases associated with drugs, infections, or neoplasia. The cause of idiopathic nephrotic syndrome remains unknown, but evidence suggests it may be a primary T-cell disorder that leads to glomerular podocyte dysfunction. Genetic studies in children with familial nephrotic syndrome have identified mutations in genes that encode important podocyte proteins. Patients with idiopathic nephrotic syndrome are initially treated with corticosteroids. Steroid-responsiveness is of greater prognostic use than renal histology. Several second-line drugs, including alkylating agents, ciclosporin, and levamisole, may be effective for complicated and steroid-unresponsive MCNS and FSGS patients. Nephrotic syndrome is associated with several medical complications, the most severe and potentially fatal being bacterial infections and thromboembolism. Idiopathic nephrotic syndrome is a chronic relapsing disease for most steroid-responsive patients, whereas most children with refractory FSGS ultimately develop end-stage renal disease. Research is being done to further elucidate the disorder's molecular pathogenesis, identify new prognostic indicators, and to develop better approaches to treatment.

The first recorded description of nephrotic syndrome dates to the 15th century. Later, Volhard and Fahr[1] popularised the term nephrosis, using it to describe a major classification of bilateral renal disease. Today, nephrotic syndrome is recognised as a common chronic illness in childhood. The constellation of features that characterise nephrotic syndrome develops from primary alterations of the permselectivity barrier of the glomerular capillary wall, which is no longer able to restrict the loss of protein to less than 100 mg/m^2 body surface per day. Nephrotic-range proteinuria has been variously defined, including the increasingly popular use of spot urinary protein-to-creatinine ratio higher than 0·25 g protein per mmol creatinine (or >2·0 mg protein per mg creatinine). Although nephrotic syndrome may be associated with many renal diseases, the most common form in childhood is primary nephrotic syndrome, which develops in the absence of features of nephritis or associated primary extrarenal disease (panel 1). Less commonly, childhood nephrotic syndrome is the consequence of an inflammatory or ischaemic glomerular disorder or is due to an inherited renal disease. Although the pathogenesis of idiopathic childhood nephrotic syndrome remains unclear, important clues have surfaced, including the identification of several inherited mutations in genes that encode functionally important glomerular epithelial-cell (podocyte) proteins.

Epidemiology and classification

Idiopathic nephrotic syndrome has a reported incidence of two to seven cases per 100 000 children and a prevalence of nearly 16 cases per 100 000. There are three distinct histological variants of primary idiopathic nephrotic syndrome: minimal-change nephrotic syndrome (MCNS), focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (figure 1). MCNS and FSGS may represent opposite ends of one pathophysiological process or distinct disease entities. By contrast, membranous nephropathy is a distinct disease associated with prominent immune complex deposits located between glomerular podocytes and the glomerular basement membrane. Membranous nephropathy is rare in children.

Although the overall incidence of childhood idiopathic nephrotic syndrome has been generally stable over the past three decades,[2] the histological pattern is changing. The incidence of FSGS seems to be increasing, in children and adults, even after adjustment for changes in renal biopsy practices (table 1).[3–6] Ethnic origin may affect the histological variant and the response to immunosuppressive treatment. In particular, Hispanic and black patients are more likely to have steroid-unresponsive nephrotic syndrome than are white patients.[7] Age at initial presentation has an important impact on the disease distribution frequency. 70% of MCNS patients are younger than 5 years; 20–30% of adolescent nephrotic patients have MCNS.[8] FSGS develops in children at a median age of 6 years.[3] During the first year of life, congenital (birth to age 3 months) and infantile (3–12 months) genetic disorders and congenital

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Search strategy

We searched the PubMed on-line database for all English-language papers on nephrotic syndrome published between 1996 and 2002. Our key search terms were "nephrotic syndrome", limited to "all children". We chose papers relevant to the paediatric population and pertaining to the topics of epidemiology, pathophysiology, diagnosis, and management as the basis of further review for this seminar.

Panel 1: **Causes of childhood nephrotic syndrome***

Genetic disorders

Nephrotic-syndrome typical
Finnish-type congenital nephrotic syndrome
FSGS
Diffuse mesangial sclerosis
Denys-Drash syndrome
Schimke immuno-osseous dysplasia

Proteinuira with or without nephrotic syndrome
Nail-patella syndrome
Alport's syndrome

Multisystem syndromes with or without nephrotic syndrome
Galloway-Mowat syndrome
Charcot-Marie-Tooth disease
Jeune's syndrome
Cockayne's syndrome
Laurence-Moon-Biedl-Bardet syndrome

Metabolic disorders with or without nephrotic syndrome
Alagille syndrome
α-1 antitrypsin deficiency
Fabry disease
Glutaric acidaemia
Glycogen storage disease
Hurler's syndrome
Lipoprotein disorders
Mitochondrial cytopathies
Sickle-cell disease

Idiopathic nephrotic syndrome
MCNS
FSGS
Membranous nephropathy

Secondary causes

Infections
Hepatitis B, C
HIV-1
Malaria
Syphilis
Toxoplasmosis

Drugs
Penicillamine
Gold
Non-steroidal anti-inflammatory drugs
Pamidronate
Interferon
Mercury
Heroin
Lithium

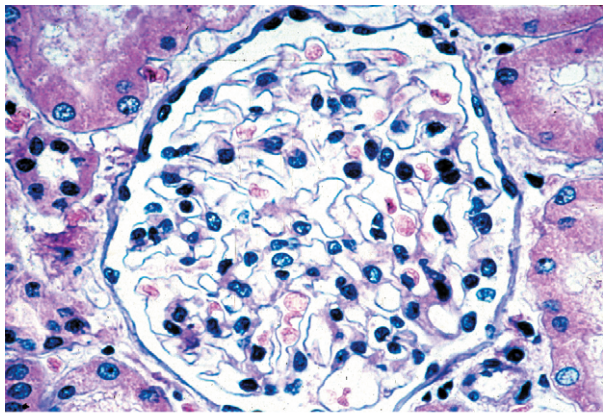
Immunological or allergic disorders
Castleman's disease
Kimura's disease
Bee sting
Food allergens

Associated with malignant disease
Lymphoma
Leukaemia

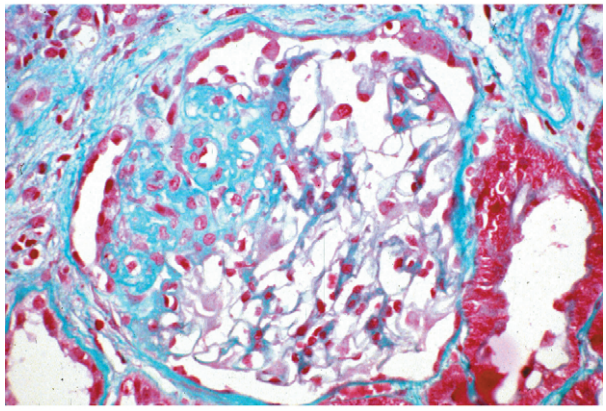
Glomerular hyperfiltration
Oligomeganephronia
Morbid obesity
Adaptation to nephron reduction

*May also be consequence of inflammatory glomerular disorders, normally associated with features of nephritis—eg, vasculitis, lupus nephritis, membranoproliferative glomerulonephritis, IgA nephropathy.

MCNS



FSGS



Membranous nephropathy

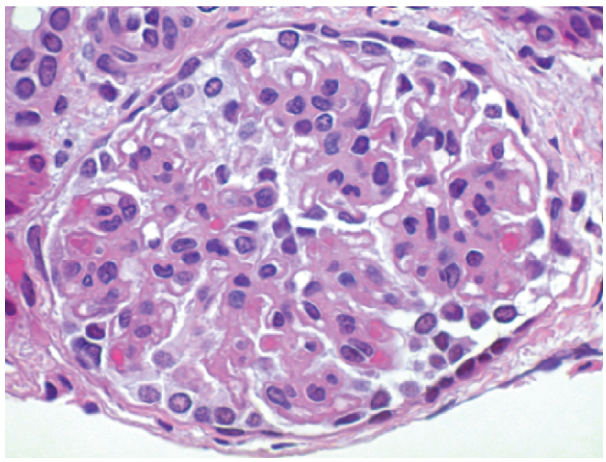


Figure 1: **Histopathology slides from children with MCNS, FSGS, and membranous nephropathy**

infections are much more common than MCNS and FSGS. Inherited forms of steroid-responsive and steroid-resistant nephrotic syndrome are being increasingly recognised.

Not all cases of MCNS or FSGS are idiopathic (panel 1). MCNS can occur in association with lymphoid tumours or immunomodulatory drugs. FSGS is the most common histological variant in patients with HIV nephropathy. Renal lesions resembling idiopathic FSGS may also be present in proteinuric patients with other primary renal disorders, such as chronic glomerulonephritis, reflux nephropathy, and oligo-meganephronia.

	Era 1		Era 2	
	Dates	n (%)	Dates	n (%)
Population				
India (biopsies)[4]	Jan 1990–June 1992	65 (20)	July 1992–Dec 1996	157 (47)
USA (biopsies)[5]	Before 1990	68 (23)	After 1990	36 (47)
North America,[2] and Hong Kong[3] (all cases)	1967–74	521 (7)	1984–95	148 (23)
Saudi Arabia (all cases)[6]	1983–92	132 (5)	1997–2001	46 (15)

Table 1: **Increase in incidence of childhood nephrotic syndrome due to FSGS**

Pathogenesis and pathophysiology

Primary glomerular defect

The glomerular capillary wall consists of three structural elements that constitute the permselectivity barrier: endothelial cells separated by fenestrae, the glomerular basement membrane made up of a network of matrix proteins, and specialised epithelial cells (podocytes) connected to each other via an interdigitating network of slit diaphragms. Normally, proteins the size of albumin (69 kd) and larger are excluded from filtration, a restriction that depends substantially on the integrity of the slit diaphragms. In nephrotic syndrome, glomeruli appear greatly changed—adjacent podocytes appear fused together, assuming a flattened rather than foot-like morphology (figure 2).

Three observations provide important clues to the primary pathophysiology of idiopathic nephrotic syndrome. Mutations in several podocyte proteins have been identified in families with inherited nephrotic syndrome, highlighting the central importance of the podocyte (figure 2). A plasma factor may alter glomerular permeability, especially among patients with steroid-resistant nephrotic syndrome. Altered T-lymphocyte responses seem to be important; a primary T-cell event could result in the production of a permeability factor that interferes with the expression, function, or both, of key podocyte proteins to cause proteinuria. The podocyte target of such a putative factor is, however, unclear. A higher rate of certain gene polymorphisms among nephrotic patients than among controls suggests the existence of disease susceptibility genes (figure 3). Risk of progressive FSGS may also be determined by genotype.

Nephrin was the first slit-diaphragm protein identified (figure 2, table 2).[9–19] Mutations in this transmembrane protein cause congenital (Finnish-type) nephrotic syndrome that occurs with a frequency of one per 8200 livebirths in Finland. Among children with inherited nephrotic syndrome, investigators have identified mutations in other genes that encode podocyte proteins (figure 2, table 2). Many laboratories are actively investigating how disruptions in the podocyte network (from the slit diaphragm to its contractile cytoskeleton) cause pathological proteinuria.

The role of podocyte proteins in the pathogenesis of sporadic cases of so-called idiopathic nephrotic syndrome requires further investigation. Genetic mutations have been identified in some children with sporadic steroid-resistant nephrotic syndrome. In particular, mutations in the gene encoding podocin have been identified in patients with sporadic FSGS;[20–22] mutations in *WT-1* have been reported in children with isolated diffuse mesangial sclerosis.[23,24] Steroid-responsive nephrotic syndrome is occasionally seen in more than one family member. At least one locus has been mapped to chromosome 1q25, close to but distinct from the podocin gene.[25]

Circulating permeability factor and inhibitors

A soluble factor produced in nephrotic syndrome has long been proposed to mediate changes in the capillary wall and lead to albuminuria.[26,27] The most compelling evidence comes from experience with renal allografts: nephrotic syndrome disappears when an MCNS kidney is transplanted into a patient without nephrotic syndrome; FSGS may recur (frequently within hours) when a normal kidney is transplanted into a patient who has end-stage renal disease due to FSGS.[28] The nature of this permeability-modifying factor remains unknown, although several candidates have been proposed.

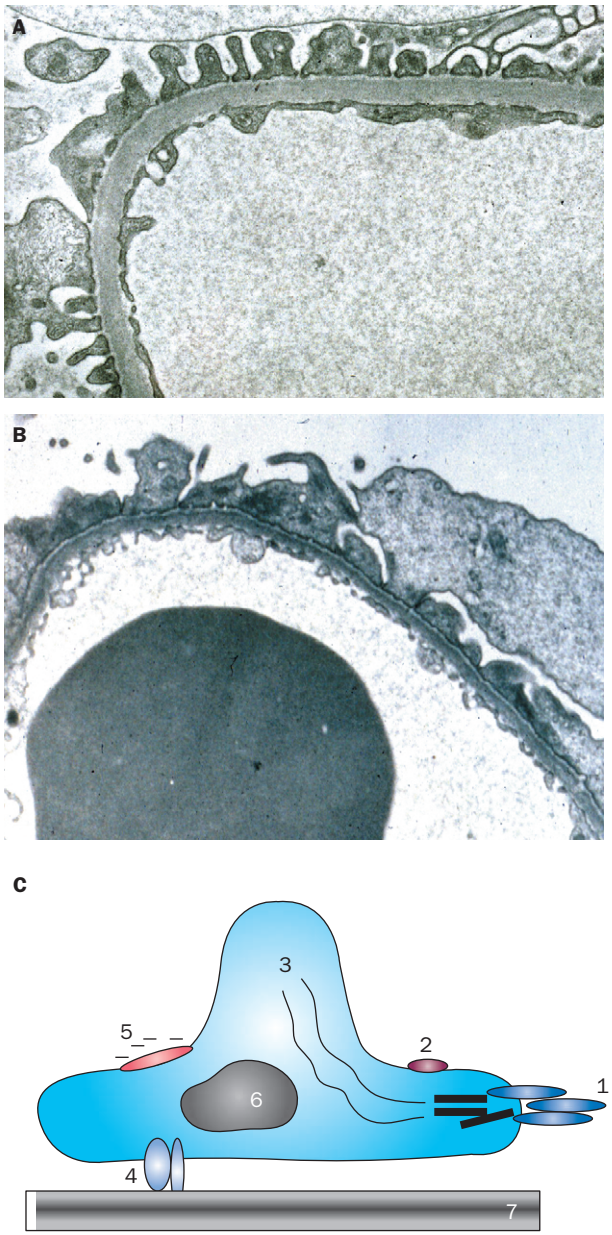


Figure 2: **Electron microscopic appearance of normal glomerular epithelial cells in normal epithelial cells and nephrotic syndrome, and mutations in podocyte proteins**
A: Individual foot processes of normal glomerular epithelial cells (podocytes) are separated by slit pores, crossed by slit diaphragms. B: In nephrotic syndrome, slit pores disappear and foot processes assume fused appearance. C: Mutations have been identified in inherited diseases associated with nephrotic syndromes. 1=slit diaphragm proteins (nephrin). 2=membrane proteins (podocin). 3=cytoskeleton (α-actinin-4, CD2-AP). 4=extracellular matrix adhesion molecules (β4 integrin). 5=sialylated anionic surface proteins. 6=nuclear proteins (WT1, LMX1B, SMARCAL1). 7=basement membrane proteins (α5 chain collagen IV).

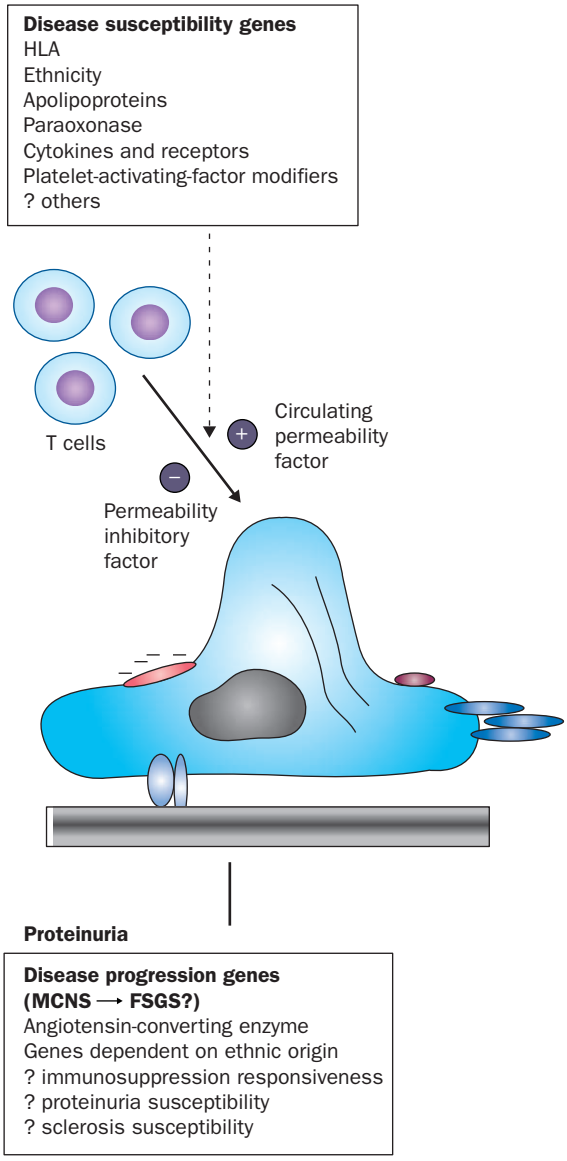


Figure 3: **Summary of proposed pathogenetic paradigms for idiopathic nephrotic syndrome**
T cells presumed to synthesise an as-yet unidentified circulating permeability factor that alters the normal glomerular protein permselectivity barrier resulting in high-grade proteinuria. T-cell process may inhibit or down-regulate a permeability inhibitory factor that normally prevents proteinuria. Podocyte target is currently unclear.

One permeability factor that has received a lot of attention was first identified in the plasma of FSGS patients by Savin and Sharma.[29] This factor exerts permeability changes in cultured rat glomeruli and is associated with a substantial risk of recurrence of FSGS in a renal allograft. The therapeutic use of plasma exchange is plausible in such patients. To date, the factor itself has not been identified. Since the permeability factor can also be removed by immunoabsorption to protein A, it may circulate in association with IgG.[30] This factor may cross the placenta to induce transient neonatal proteinuria.[31] Permeability activity has been identified in plasma from patients with podocin mutations, which suggests that this factor is not unique to idiopathic FSGS.[32] Altered glomerular permeability can be corrected in vitro by addition of nephrotic but not normal urine; therefore, an inhibitory substance might be lost in the urine of nephrotic patients.[32] The findings of Candiano and colleagues[33] suggest that components of high-density lipoprotein inhibit the glomerular permeability factor.

Possible immunological basis for nephrotic syndromes?

The putative permeability factor seems to be derived from lymphoid cells. The association of nephrotic syndrome with primary immunological disorders such as lymphoma, leukaemia, thymoma, Kimura's disease, and Castleman's disease, and therapeutic agents such as interferon support this hypothesis. Cultured T cells isolated from nephrotic patients have been reported to synthesise a factor or factors that produce transient proteinuria when injected into rats[34] or impair glomerular podocyte synthesis of glycosaminoglycans.[35] Still unclear is whether MCNS can occur as a manifestation of a primary allergic disorder. Although several anecdotal case reports have been published and serum IgE concentrations are frequently increased in nephrotic syndrome, therapeutic approaches based on the identification and elimination of the triggering allergen are rarely effective.[36,37] The unchanging incidence of MCNS in the past few decades, despite the increasing prevalence of allergic disorders, calls into question the strength of this association.[38] The molecular link between the immune system and idiopathic nephrotic syndrome remains unclear, despite notable differences between phenotype, cytokine expression profile, and function of lymphocytes when compared during relapse and remission having been shown in many studies.[39–44]

In response to an apparent rising incidence of FSGS, investigators have used modern molecular diagnostic tools to identify a possible infectious cause for FSGS. Such studies have provided insights into HIV nephropathy, which shows the presence of HIV genome in renal tubular

Gene	Name	Location	Inheritance	Renal disease
Steroid-resistant nephrotic syndrome				
NPHS1	Nephrin	19q13.1	Recessive	Finnish-type congenital nephrotic syndrome[9]
NPHS2	Podocin	1q25	Recessive	FSGS[10]
FSGS1	α-actinin-4 (α*ACTN4*)	19q13	Dominant	FSGS[11]
FSGS2	Unknown	11q21–22	Dominant	FSGS[12]
WT1	Wilms' tumour-suppressor gene	11p13	Dominant	Denys-Drash syndrome with diffuse mesangial sclerosis;[13,14] Frasier's syndrome with FSGS[15]
LMX1B	LIM-homoeodomain protein	9q34	Dominant	Nail-patella syndrome[16]
SMARCAL1	SW1/SNF2-related, matrix-associated, actin-dependent regulator of chromatin, subfamily a-like 1	2q35	Recessive	Schimke immuno-osseous dysplasia with FSGS*[17]
Steroid-responsive nephrotic syndrome				
Unknown	Unknown	Unknown	Recessive	MCNS

*Podocyte expression of *SMARCAL1* presumptive but not yet established. Mutations in another protein, CD2-AP or NEPH1 (novel protein structurally related to nephrin) cause congenital nephrotic syndrome in mice (reference 18). A mutational variant in the *CD2AP* gene has been identified in a few patients with steroid-resistant nephrotic syndrome (reference 19).

Table 2: **Nephrotic syndrome in children due to genetic disorders of the podocyte**

Panel 2: Features suggesting a diagnosis other than idiopathic MCNS

- Age <1 year
- Positive family history
- Extrarenal disease (eg, arthritis, rash, anaemia)
- Chronic disease
- Symptoms due to intravascular volume expansion (eg, hypertension, pulmonary oedema)
- Renal failure
- Active urine sediment (red blood cell casts)

cells and podocytes.[45] Other viral genomes have been identified in patients who have apparent idiopathic FSGS, including parvovirus 19,[46] SV40,[47] and hepatitis C.[48]

Oedema

The principal clinical manifestation of nephrotic syndrome is oedema, the pathogenesis of which remains controversial. Traditional teaching supports the so-called underfill theory, in which proteinuria and subsequent hypoalbuminaemia lead to decreased intravascular oncotic pressure. This pressure results in translocation of plasma water into the interstitial space; secondary sodium retention develops to compensate for intravascular volume contraction. The underfill theory is intuitively attractive and data showing that nephrotic patients have contracted intravascular volume, reduced glomerular filtration rate, and raised renin and aldosterone concentrations support the concept.[49]

Critics of the underfill theory point to studies in which some nephrotic patients have normal or even increased intravascular pressure.[50,51] Plasma renin activity is not universally increased in nephrotic patients.[52] Volume expansion and head-out water immersion do not consistently suppress the neurohumoral response and cause natriuresis, as would be expected if the plasma volume were contracted.[53,54]

The overfill theory, proposed in response to these criticisms, suggests that the abnormality leading to nephrotic oedema is a primary defect in sodium excretion.[55] The observation that in rats with unilateral proteinuria, sodium avidity is increased in only the proteinuric kidney provides experimental support.[56] The cause of the increased sodium retention remains unknown, but is thought to occur in the distal tubules, perhaps mediated by resistance to atrial natriuretic peptide.[57]

Although the overfill theory is gaining favour, it is not universally accepted and may not be sufficient to explain oedema formation in childhood nephrotic syndrome.[58] Studies of children with MCNS in particular report variability in measurements of intravascular volume status. The underfill and overfill mechanisms are not necessarily mutually exclusive, dependent on the stage of nephrotic syndrome, the rate of development of hypoproteinaemia, and absolute plasma oncotic pressure.[59] Children with MCNS frequently present with rapid onset of proteinuria and oedema formation; intravascular volume contraction (underfill) is common in this acute setting but may be less operant later in their course. By contrast, patients with chronic forms of persistent nephrotic syndrome may have continuing sodium retention and thus be more prone to oedema from overfill mechanisms.

Hyperlipidaemia

Hyperlipidaemia, with raised serum cholesterol and triglyceride concentrations, is a hallmark of nephrotic syndrome. This complication results from complex interactions between disordered lipoprotein metabolism, medications, and dietary factors. Increased hepatic lipoprotein synthesis, in response to low plasma oncotic pressure, as a consequence of the urinary loss of an as-yet unidentified regulatory substance, or both, is thought to play a key pathogenetic part.[60] Studies in experimental nephrotic syndrome models have identified several enzymatic changes that alter lipid biosynthesis and degradation. These include increased hepatic 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and acyl-coenzyme A-cholesterol acyltransferase activities, and decreased cholesterol 7 α hydroxylase and lipoprotein lipase activities.[61–63] Variability of apolipoprotein (a) may also contribute to differences in lipid concentrations during active nephrotic syndrome and remission.[64]

Diagnosis

Once diagnosed, a series of questions should be asked to establish a cause for the nephrotic syndrome (panel 1). Since MCNS is by far the most common cause of nephrotic syndromes in childhood, initial efforts are devoted to the detection of features that are atypical of MCNS (panel 2). A course of corticosteroid treatment without a renal biopsy is indicated for children without atypical features, since responsiveness to steroids is a better indicator than kidney histology of long-term prognosis for renal function. Renal biopsy is generally limited to steroid-unresponsive and steroid-dependent patients, although it has yet to be shown that this information affects outcome.[65,66] Most centres also recommend biopsy before the use of nephrotoxic treatments such as ciclosporin.

Management

This section will focus on the current treatment options for children with idiopathic nephrotic syndrome due to MCNS and FSGS. Given the rare occurrence of idiopathic membranous nephropathy in children, there are currently no published treatment guidelines based on randomised paediatric trials. Therapeutic approaches are extrapolated from experience with adult membranous nephropathy patients.[67]

Treatment of steroid-responsive nephrotic syndrome

Roughly 95% of patients with MCNS and 20% with FSGS achieve remission after an 8-week course of prednisone (60 mg/m^2 daily for 4 weeks followed by 40 mg/m^2 on alternate days for 4 weeks). Traditionally, patients receive divided doses but once-daily treatment also seems to be effective.[68] MCNS patients respond quite quickly—around 75% achieve remission by 2 weeks.[69] Given the high relapse rate for MCNS patients, there has been a shift in the past decade to longer courses of corticosteroid treatment for first episodes of nephrotic syndromes in an effort to decrease the relapse rate. In support of this approach was the study by the Arbeitsgemeinschaft für Pädiatrische Nephrologie,[70] in which a lower relapse rate at 1 year (36 *vs* 62%) was reported among patients treated with 60 mg/m^2 prednisone daily for 6 weeks followed by 40 mg/m^2 prednisone on alternate days for 6 weeks than among patients who received the then standard 8-week treatment.

In a meta-analysis of the five randomised controlled trials involving children with a first episode of steroid-responsive nephrotic syndrome, longer duration of treatment significantly decreased the risk of relapse at 12 and 24 months without an increase in adverse events.[71] An inverse relation was noted between the duration of

treatment and the risk of relapse, with an increase in benefit found for up to 7 months of treatment. Although 8–12 weeks total treatment is the published standard, many centres now routinely recommend 12 weeks.[72]

Frequently relapsing and steroid-dependent nephrotic syndromes

Unfortunately, around 60% of steroid-responsive patients experience five or more relapses. Some of these patients can be managed with low-dose steroids given daily or on alternate days, but many still relapse, especially if they have intercurrent infections. Steroid-induced side-effects develop in a high proportion of these patients. Currently there are no data on the preferred second-line drug. Use of cyclophosphamide, chlorambucil, ciclosporin, and levamisole to reduce the risk of relapses is supported by a systematic review of randomised controlled trials[73] and by evidence-based recommendations.[74]

Alkylating agents have been used since the 1950s. Although children in both subgroups may benefit from a course of alkylating agents, those with frequently relapsing nephrotic syndrome (two or more relapses within 6 months of initial response or four or more relapses in any 12-month period) reportedly achieve a longer remission with alkylating agents than do children with steroid-dependent nephrotic syndrome (two consecutive relapses during tapering or within 14 days of cessation of glucocorticoids).[75] Treatment with cyclophosphamide (2·0–2·5 mg/kg daily) or chlorambucil (0·2 mg/kg) is generally given for 8–12 weeks. Given the risks of seizures associated with chlorambucil, cyclophosphamide is more commonly prescribed.[76] Intravenous monthly treatment also seems effective, but there is no clear advantage.[77] Guidelines for a second course of alkylating agent need to be established. Although not commonly recommended, a second 8-week course of cyclophosphamide can be given without reaching the threshold cumulative dose of 200 mg/kg, above which the risk of gonadal toxic effects rises substantially.[78]

Ciclosporin is an important steroid-sparing agent in the treatment of steroid-responsive nephrotic syndrome.[79] Since the early reports in the late 1980s, responsiveness to ciclosporin has been confirmed in many studies and important data on safety and efficacy have been added.[80] Overall, when used to treat steroid-responsive nephrotic syndrome, remission can be achieved in 85% of patients.[81] Although there is no standard treatment protocol, initial ciclosporin treatment normally lasts for 1–2 years. Most patients can be managed with doses of 5–6 mg/kg daily and trough concentrations of 50–125 ng/mL. Concerns about nephrotoxic effects mandate careful monitoring of renal function and ciclosporin plasma concentrations. Not all ciclosporin-treated patients can discontinue steroids and maintain remission—as many as 40% may need concomitant low-dose steroids.[82] Longer-duration treatment is being used with increasing frequency but should include follow-up renal biopsies to check for evidence of ciclosporin-induced vasculopathy.[83,84]

Levamisole is an anthelmintic drug with immunostimulatory properties. Levamisole (2·5 mg/kg on alternate days) decreases the number of relapses in children with frequently relapsing nephrotic syndrome.[85] In a retrospective analysis, levamisole was suggested to be as effective as cyclophosphamide in frequently relapsing nephrotic syndrome.[86] This drug does have toxic effects (eg, leukopenia, hepatic abnormalities), including rare cases of agranulocytosis, vasculitis, and encephalopathy. Mizoribine, an immunosuppressive purine-synthesis inhibitor developed in Japan, was reported to reduce the number of relapses in children younger than 10 years if given for 48 weeks, but it did not reduce the relapse rate for the treatment group as a whole.[87] Case reports of responsiveness to mycophenolate mofetil have begun to be published, but recommendation for the use of this drug must await the results of randomised controlled clinical trials.[88]

Steroid-resistant idiopathic nephrotic syndrome

A few patients (around 20–25%) with idiopathic FSGS respond to an 8-week course of high-dose corticosteroids. Although steroid treatment is normally continued beyond 8 weeks even in steroid-resistant patients, and it remains a component of most subsequent treatment, we have no adequate evidence from randomised controlled clinical trials to provide clear guidance for subsequent dosing. The same is true for second-line drug treatment for steroid-resistant patients. Three options are frequently considered: alkylating agents, calcineurin inhibitors, and high-dose pulse methylprednisolone (mostly in combination with an alkylating agent).

Indications for the use of alkylating agents are somewhat controversial. In a summary of nine paediatric series published in 1984, 30% of steroid-unresponsive patients responded to cyclophosphamide.[89] In a later randomised prospective study of 60 children, the remission rate was similar in the steroid-only group and the steroid plus cyclophosphamide group (28 *vs* 25%).[90] Although monthly intravenous cyclophosphamide may also induce remission, whether this route of administration is safer or more effective has not been shown.[91] The subset of children who have a partial response to steroids has not been analysed systematically, but, anecdotally, many of these patients are cyclophosphamide responsive.

Calcineurin inhibitors, especially ciclosporin, have become the most commonly used second-line drugs in many centres, based on the observation that 20–30% of paediatric FSGS patients are ciclosporin responsive.[92–94] In a randomised trial in adults with steroid-resistant FSGS, 12% achieved complete remission and 70% complete or partial remission.[95] Even a partial response improves long-term prognosis. Standardised guidelines for the dose and duration of treatment are not available. To achieve remission, the initial target plasma trough concentrations may need to be higher than those commonly used in the treatment of steroid-responsive patients, and several years of treatment may be necessary. A theoretical concern, based on the lipophilic nature of ciclosporin, is that much higher plasma concentrations may be necessary to achieve adequate tissue ciclosporin concentrations.[96] This hypothesis has never been properly tested. A difficult question is when to abandon ciclosporin treatment and declare a patient a non-responder to this drug. A trial period of 6 months is commonly used.[97] A few anecdotal cases have reported success with tacrolimus after ciclosporin failure.[98,99]

To date, the highest response rate for FSGS patients has been reported with high-dose pulse methylprednisolone given in a tapering schedule over 72 months.[100,101] Most patients also receive alkylating agents if urinary protein-to-creatinine ratios do not decrease within a few weeks. Despite the very promising initial outcome reported with this therapeutic protocol, not all subsequent case series have reported similar results. Ethnic composition of the study population is an important factor, since black and Hispanic patients are less responsive than patients of other ethnic origins.[7] This treatment protocol has not yet been subjected to the

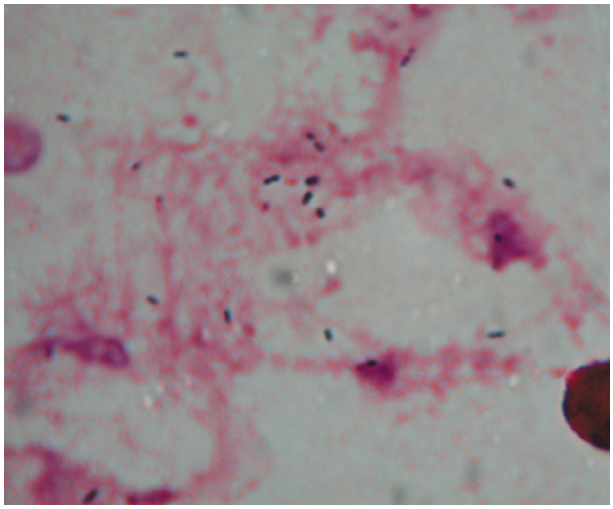


Figure 4: ***Streptococcus pneumoniae* Infection as a complication in immunocompromised nephrotic syndrome**
Defective opsonisation (low factor B and I concentrations), altered T-cell function, altered IgG concentrations (total and subclass changes), immunosuppressive therapy, and mechanical factors (oedema, ascites).

rigour of a randomised prospective clinical trial to find out whether it is more effective than other regimens. Given the potential for steroid-induced toxic effects, many centres view such aggressive treatment cautiously. However, with the high rate of end-stage renal disease among patients unresponsive to traditional doses of glucocorticoids and ciclosporin, this approach is often considered.

New therapeutic approaches are needed for steroid-resistant FSGS patients, but these must undergo testing in randomised prospective clinical trials. Meanwhile, historical controls are being used in some centres to find out whether plasmapheresis or immunoadsorption (to remove a putative pathogenic circulating permeability factor)[102–104] or newer immunosuppressive agents (such as mycophenolate mofetil and sirolimus)[88] have a place in the treatment of idiopathic primary FSGS. Drug inhibitors of angiotensin II are currently the antihypertensive drugs of choice for FSGS patients given these drugs' potential to independently reduce protein excretion rates and to inhibit the fibrogenic growth factor transforming growth factor β.[105] Interest has increased in the use of these agents for treatment-resistant FSGS patients even in the absence of hypertension,[106] but their efficacy as renoprotective agents in normotensive patients is largely based on animal studies.[107,108]

Complications of nephrotic syndrome

Medical complications of nephrotic syndrome are potentially serious. They can be divided into two major subgroups: acute complications related to the nephrotic state, especially infections and thromboembolic disease, and long-term sequelae of nephrotic syndrome and its treatment, especially effects on bones, growth, and the cardiovascular system. A third important area is the psychological impact and social demands on children who have nephrotic syndrome, and their families.[109]

Infectious complications

Serious infection, especially cellulitis and spontaneous bacterial peritonitis, can complicate nephrotic syndrome. The rate of peritonitis is 2–6%,[110] and overwhelming infection still carries a mortality rate of 1·5%.[111] Susceptibility to bacterial infection is related to multiple predisposing factors (figure 4). Impaired complement-dependent opsonisation delays clearance of encapsulated micro-organisms, especially *Streptococcus pneumoniae* (figure 4).[112] Pneumococcal vaccination is recommended for patients who have nephrotic syndrome.[113] Prophylactic treatment with penicillin during relapses has been suggested but few data support this practice.[114] Patients are also predisposed to gram-negative bacterial infections.[115]

Since many children with idiopathic nephrotic syndrome are varicella non-immune, varicella exposure and infection require special consideration. Prophylactic treatment with varicella zoster immune globulin is recommended for non-immune patients taking immunosuppressive treatments.[116] Once remission is achieved, immunisation with varicella vaccine seems safe and effective, although additional doses may be required to achieve full immunity.[117,118] Concomitant use of oral aciclovir may also prevent serious varicella infection in patients receiving corticosteroids.[119]

Thromboembolic complications

Nephrotic patients are at significantly increased risk of thrombosis, with complication rates reported as high as 40% in adults.[120] Although thrombosis risk is apparently lower in nephrotic children (1·8–5·0%), these events can be severe.[121] Multiple factors contribute to the dysregulated coagulation state of nephrotic syndrome (figure 5). No one laboratory test can reliably predict the real thrombotic risk. Fibrinogen concentration has been proposed as a surrogate marker. Other factors that increase thrombotic risk in nephrotic patients include diuretic use, corticosteroid treatment, immobilisation, and the presence of in-dwelling catheters. If a clot is noted in a nephrotic child, investigation for an inherited coagulation abnormality is still recommended. Prophylactic anticoagulation is not recommended because of its own inherent risks. However, after treatment of a documented clot, use of prophylactic warfarin has been recommended for at least 6 months, and perhaps during future relapses.[122] In-dwelling venous catheters should be avoided, but if absolutely necessary, prophylactic anticoagulation should be considered. Low-molecular-weight heparin is an attractive alternative agent, but it requires sufficient antithrombin III substrate to be effective.[122] Aspirin may also be considered for anticoagulation, especially if thrombocytosis is severe.

Figure 5: **Acute main pulmonary artery thrombosis as a complication in prothrombotic state of nephrotic syndrome**
Increased clotting factor synthesis (fibrinogen, II, V, VII, VIII, IX, X, XIII), urinary loss of anticoagulants (antithrombin III), platelet abnormalities (thrombocytosis, increased aggregability), hyperviscosity, and hyperlipaemia. Reproduced from Jones CL, Hébert D. Pulmonary thromboemboli in the nephrotic syndrome. *Pediatr Nephrol* 1991; **5:** 56, with copyright permission from Springer-Verlag, Heidelberg, Germany.

Cardiovascular disease

Multiple factors raise concerns for cardiovascular sequelae in children with long-term nephrotic syndrome, including exposure to corticosteroids, hyperlipidaemia, oxidant stress, hypertension, hypercoagulability, and anaemia (erythropoietin-responsive anaemia is a rare complication[123,124]). Nephrotic syndrome in adulthood is associated with an increased risk of coronary heart disease.[125] Myocardial infarction in young children with nephrotic syndrome has been reported, but the relative risk has not been calculated.[126] In adults with nephrotic syndrome, HMG-CoA-reductase inhibitors can control hyperlipidaemia and limit its complications.[127–129] Whether or not to treat hyperlipidaemia in nephrotic children has been a source of controversy, especially since most children have treatable renal disease.[60] Adequate safety and efficacy data for HMG-CoA-reductase inhibitors in children are not available, despite small case series in which decreased serum lipids have been reported.[130,131] Persistent hyperlipidaemia in unremitting childhood nephrotic syndrome is concerning, but there is little evidence as yet to guide treatment or predict future outcome.

Other medical complications

Despite theoretical risks of bone-density reduction with corticosteroid use, the prevalence of bone disease in children with nephrotic syndrome is not yet clear. In addition to steroids, there are other potential causes of bone disease in nephrotic syndrome. Urinary loss of vitamin-D-binding protein, a 59 kd carrier protein for 25-hydroxycholecalciferol, may cause vitamin D deficiency and, less commonly, secondary hyperparathyroidism.[132–134] Other potential medical complications include drug toxic effects, hypothyroidism[135] and acute renal failure.[136] Although diuretics and albumin infusions can successfully treat symptomatic oedema, injudicious use can lead to either acute volume overload or intravascular depletion, dependent on the cause of oedema.

Natural history and prognosis

The most important prognostic indicator in nephrotic syndrome is steroid responsiveness. Overall, 60–80% of steroid-responsive nephrotic children will relapse and about 60% of those will have five or more relapses. Age older than 4 years at presentation and remission within 7–9 days of the start of steroid treatment in the absence of microhaematuria are predictive of fewer relapses.[137–139] In a natural-history study of 398 children, the proportion that became non-relapsers rose from 44% at 1 year to 69% at 5 years, and 84% at 10 years.[140]

For the steroid-resistant FSGS patients, the clinical course is typically very challenging. With current treatments, a few children will ultimately achieve a sustained remission with one of the second-line or third-line drugs. For patients with refractory nephrotic syndrome, progression to end-stage renal disease is inevitable. Some of these children have such a difficult clinical course because of refractory oedema, severe infections, thromboembolic complications, or a combination of these, that bilateral nephrectomies and dialysis provide welcome relief. For this subgroup, the ultimate treatment goal is renal transplantation, despite the haunting reality that FSGS will recur in about 25% of renal allografts.[28]

For patients who have familial forms of nephrotic syndrome, immunosuppressive treatment is ineffective; definitive treatment requires renal transplantation. Most of these patients do well after transplantation. Although the original genetic renal disease does not recur in the renal allograft, nephrotic syndrome has been noted in a subset of patients as a consequence of immunological attack on a new antigen encountered for the first time in the transplanted kidney (eg, injury mediated by antibody to nephrin in children with congenital nephrotic syndrome).

Although much has been learned about the management of childhood nephrotic syndrome, this chronic disorder remains challenging. Advances in molecular genetics offer hope of new pathogenetic insights. Multicentre clinical trials are needed to improve current treatments and prevent acute and long-term complications.

Conflict of interest statement

None declared.

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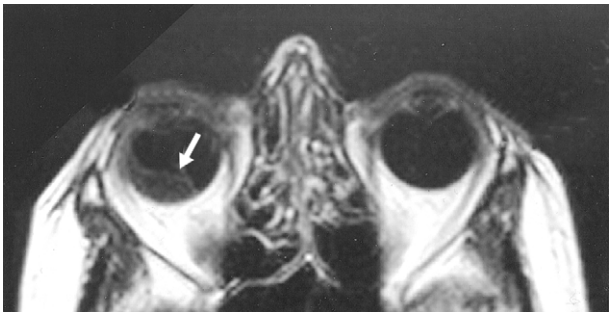
Clinical picture

Retinal detachment

Jennifer Ng, James Cleland, Peter Bergin



A 75-year-old woman presented with a 6-week history of seeing "raindrops and triangles" throughout her field of vision, which progressed to near-total painless visual loss in the right eye 4 days before presentation. On examination we found mild bilateral chemosis and subtle proptosis of the right eye. She was able to count fingers in the temporal field of her right eye, while in the nasal field she was unable to perceive light. Initial fundoscopy through the undilated pupil showed only a benign pigmented lesion over the right optic disc. The visual acuity of her left eye was normal, as was the remainder of the examination. Magnetic resonance imaging of the brain and orbits, done to exclude a retro-orbital mass lesion, showed retinal detachment in the right eye (figure, arrow). The patient had surgery with part recovery of her vision.

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