

The Nephrotic Syndrome

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Objectives After completing this article, readers should be able to:

1. Explain the mechanism and the consequences of proteinuria.
2. Make a presumptive diagnosis of minimal-change nephrotic syndrome.
3. Interpret the signs associated with steroid resistance.
4. Ascertain the timing and the indications for a kidney biopsy.
5. Gauge the indications for referral to a pediatric nephrologist.
6. Determine the adequacy of the therapy.
7. Predict the disease course.

Introduction

The word “nephrosis” was introduced in the medical literature at the beginning of the 20th century in an attempt to distinguish diseases of the kidney characterized by exudation and proliferation from those characterized by inflammation (nephritis). As it became apparent that this is not a single disease, not even a group of related diseases, the term “nephrosis” was supplanted by “nephrotic syndrome.” The clinical features that characterize the nephrotic syndrome result from alterations of the glomerular capillary wall and consist of heavy proteinuria and hypoalbuminemia, often associated with edema and generalized hyperlipidemia.

Pathophysiology

Proteinuria and Hypoalbuminemia

Proteinuria is the result of alterations in the integrity of the glomerular filtration barrier. This barrier is composed of three layers in series: the fenestrated endothelium, the glomerular basement membrane, and the visceral glomerular epithelium, comprised of podocytes and their slit diaphragms. Podocyte is the name of the epithelial cell, and foot process is the segment of the cell that extends into the urinary space. (In the nephrotic syndrome, there is effacement of the foot process, but the rest of the cell usually is preserved.)

Endothelial cells have numerous openings that are 70 to 100 nm in diameter, called fenestrae, which form a physical barrier for passage of macromolecules from plasma into the renal tubule. Electron microscopic studies led to the identification of negatively charged particles (heparan sulfate proteoglycans) in the glomerular basement membrane, which preclude the passage of anionic macromolecules, such as albumin. Removal of these charges in animals by in situ perfusion of heparitinase resulted in proteinuria.

Until recently, the podocytes were considered to play a passive role in the process of glomerular filtration. This concept changed dramatically with the discovery that muta-

Abbreviations

ACE:	angiotensin-converting enzyme
BSA:	body surface area
CNF:	congenital nephrotic syndrome of the Finnish type
CNS:	congenital nephrotic syndrome
FSGS:	focal segmental glomerulosclerosis
HDL:	high-density lipoprotein
Ig:	immunoglobulin
IL:	interleukin
ISKDC:	International Study of Kidney Disease in Children
LDL:	low-density lipoprotein
MCNS:	minimal-change nephrotic syndrome
MN:	membranous nephropathy
MPGN:	mesangioproliferative glomerulonephritis
RAA:	renin-angiotensin-aldosterone
SLE:	systemic lupus erythematosus
UPr/Cr:	urine protein/creatinine ratio
VLDL:	very low-density lipoprotein

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tion of a protein located at the slit diaphragm, named nephrin, is the cause of the congenital nephrotic syndrome of the Finnish type (CNF). (1) The slit diaphragm is a thin membrane that bridges the filtration pores between adjacent podocytes and is anchored to the cell cytoskeleton by adaptor proteins such as podocin and CD2AP. Podocytes have been found to affect the structure and function of the glomerular basement membrane and to regulate the integrity and survival of glomerular endothelial cells. A number of acquired and inherited diseases now are attributed to defects of the slit diaphragm protein complex (Table 1).

Edema

The classic theory is that edema formation results from a decrease in plasma oncotic pressure due to loss of serum albumin, causing water to extravasate into the interstitial space. Such movement reduces the intravascular volume, leading to renal hypoperfusion and stimulation of the renin-angiotensin-aldosterone (RAA) system. Aldosterone increases reabsorption of sodium, particularly at the level of the distal segments of the nephron. This hypothesis, although attractive, is not supported fully by clinical findings. Plasma volume has been shown to be decreased only in some children who have minimal-change nephrotic syndrome (MCNS), particularly during the initial phase of a relapse. The decrease is absent in others and almost always absent in adults who have nephrotic syndrome. In addition, studies have failed to demonstrate elevation of RAA hormones, and increased sodium reabsorption was found to continue when albumin was infused or angiotensin-converting enzyme (ACE) inhibitors were administered to suppress renin production. An intrinsic renal abnormality leading to

retention of sodium is postulated. Vasopressin excess also contributes to the retention of water.

Hyperlipidemia

Increased concentrations of very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) result in elevated serum cholesterol and triglycerides concentrations. The high-density lipoprotein (HDL) fraction is normal. Consequently, the LDL/HDL cholesterol ratio is increased. Several mechanisms allegedly contribute to nephrotic syndrome dyslipidemia: overproduction due to low plasma albumin concentration and low oncotic pressure and impaired catabolism of apolipoprotein B and VLDL chylomicrons.

Epidemiology

The incidence of idiopathic nephrotic syndrome in the United States has been reported to be 2.7 new cases per 100,000 children per year, and the cumulative prevalence rate is 16 per 100,000 children. The ratio of males to females is approximately 2:1 during childhood, but the sex difference wanes by adolescence. There is an increased familial incidence, particularly among siblings. The mean age at onset has been reported to be 3.4 years in Asians and 4.2 years in Europeans. Compared with other populations, African American and Hispanic children have a greater incidence of nephrotic syndrome, a more severe form of disease, and a poorer prognosis. (2)

Classification

Nephrotic syndrome can be primary (idiopathic) or secondary. Among children, 90% of cases are primary and the rest are secondary (Table 2). The advent of percutaneous renal biopsy in the 1950s and 1960s led to the identification of three histologic types of idiopathic nephrotic syndrome: MCNS, focal segmental glomerulosclerosis (FSGS), and membranous nephropathy (MN). Whereas the incidence of nephrotic syndrome has remained stable for decades, the distribution of histologic types apparently has changed due to an increase in the incidence of FSGS.

MCNS is the most common form of disease in children, accounting for approximately 85% of cases. On light microscopy, the glomeruli appear normal; electron microscopy allows detection of fusion of the epithelial foot processes, a finding common to all proteinuric states. FSGS accounts for 10% to 15% of all cases of nephrotic syndrome. Scar tissue develops initially in segments of some glomeruli, leading eventually to global,

Table 1. Genetic Forms of Nephrotic Syndrome

Gene/Protein	Location	Phenotype	Inheritance
<i>NPHS</i> /nephrin	Slit diaphragm	CNF	AR
<i>NPHS2</i> /podocin	Slit diaphragm	FSGS	AR
<i>CD2AP</i> /CD2AP	Near slit diaphragm	FSGS	
<i>TRPC6</i> /TRPC6	Podocyte	FSGS	AD
<i>WT1</i>	Podocyte	FSGS	AR
<i>ACTIN4</i>	Foot process	FSGS	AD
<i>tRNA^{Leu}</i>	Podocyte	FSGS	
<i>COQ2</i>	Podocyte	FSGS	

AD=autosomal dominant, AR=autosomal recessive, CNF=congenital nephrotic syndrome of the Finnish type, FSGS=focal segmental glomerulosclerosis

Table 2. Secondary Causes of Nephrotic Syndrome

Infections

- Hepatitis B, C
- Human immunodeficiency virus
- Malaria
- Toxoplasmosis
- Syphilis

Drugs

- Gold
- Non-steroidal anti-inflammatory drugs
- Pamidronate
- Interferon
- Heroin
- Lithium

Malignancies

- Lymphoma
- Leukemia

Miscellaneous

- Systemic lupus erythematosus
- Mesangioproliferative glomerulonephritis
- Immunoglobulin A nephropathy
- Diabetes mellitus

extensive glomerular sclerosis and tubular atrophy. MN is characterized histologically by diffuse thickening of the glomerular capillary walls and accounts for approximately 4% of nephrotic syndrome cases in children.

Other glomerulopathies that can be associated with nephrotic syndrome are mesangioproliferative glomerulonephritis (MPGN), lupus nephritis, and immunoglobulin A (IgA) nephropathy. In the first two conditions, nephritic findings (hematuria, hypertension, decreased renal function) predominate; in the third, microscopic hematuria is interspersed with episodes of macroscopic hematuria (Table 3). In all of these diseases, the occurrence of nephrotic syndrome is associated with a guarded-to-poor prognosis.

Steroid-sensitive Nephrotic Syndrome

In the 1970s, a series of prospective, controlled, multi-center studies performed under the aegis of the International Study of Kidney Disease in Children (ISKDC) resulted in a better understanding of the relationships between the clinical course and histologic characteristics of various forms of nephrotic syndrome. Definitions of terms (Table 4), such as nephrotic level albuminuria and hypoalbuminemia, response to therapy, and indications for renal biopsy, were established. Various therapeutic regimens were tested, and prevention of relapse became the primary goal of therapy for patients who had MCNS. Care shifted from the hospital to the home, with emphasis on daily monitoring of the urine to detect proteinuria and initiate prednisone therapy early. Today, hospitalization should be necessary only when there is incapacitating edema (which is preventable) or infection.

A major conclusion of these studies was that the best

Table 3. Differential Diagnosis of Nephrotic Syndrome

Diagnosis	Physical Findings	Renal Function	Serum Albumin	C3 Complement	UPr/Cr	Other
MCNS	Edema	Normal	Low	Normal	>3.0	Hyperlipidemia
FSGS	Edema	Normal or low	Low	Normal	1.0 to 3.0	Hyperlipidemia Hematuria?
CNS	Anasarca	Normal or low	Very low	Normal	>3.0	Hyperlipidemia
MN	Edema	Normal or low	Very low	Normal	>3.0	Hematuria?
MPGN	Edema?	Normal or low	Low	Low	>3.0	Hematuria Hypertension
PSGN	Edema	Low	Normal	Low	<1.0	Hematuria Hypertension
HSP	Purpuric rash Arthritis	Low	Normal or low	Normal	1.0 to 3.0	Hematuria Hypertension?
LN	Butterfly rash Arthritis	Low	Normal or low	Low	1.0 to 3.0	Hematuria Hypertension
IgA	Edema?	Normal or low	Normal or low	Normal	1.0 to 3.0	Hematuria

CNS=congenital nephrotic syndrome, Cr=creatinine, FSGS=focal-segmental glomerular sclerosis, HSP=Henoch-Schönlein purpura, LN=lupus nephritis, IgA=immunoglobulin A nephropathy, MCNS=minimal-change nephrotic syndrome, MN=membranous nephropathy, MPGN=mesangioproliferative glomerulonephritis, PSGN=poststreptococcal glomerulonephritis, UPr=urine protein

Table 4. Definition of Terms

Responder: Protein-free urine for >3 days during initial treatment

Infrequent relapser: Fewer than three relapses within 6 months of the initial response or fewer than four relapses within any 12-month period

Frequent relapser: Three or more relapses within 6 months following initial response or four relapses within any 12-month period

Steroid-dependent: Recurrence of proteinuria on alternate-day steroid therapy or within 2 weeks after cessation of treatment

Steroid-resistant: Failure to respond to initial prednisone therapy or to 4 weeks of daily prednisone for relapse

prognostic indicator in children who have nephrotic syndrome is steroid responsiveness. Ninety-five percent of children who eventually respond to steroids do so within the first 4 weeks of treatment (Fig. 1). (3) As a result of this observation, children who fulfill the clinical criteria of MCNS (heavy proteinuria, hypoalbuminemia, and hyperlipidemia) are started on prednisone therapy without undergoing a renal biopsy. A renal biopsy at the time of diagnosis is indicated for patients who have macroscopic hematuria, severe hypertension, persistent renal insufficiency, or a low serum C3 complement value (Table 5). These signs may be indicative of MPGN, systemic lupus erythematosus (SLE), or postinfectious glomerulonephritis. A biopsy also should be performed if proteinuria persists at the end of 4 weeks of daily steroid

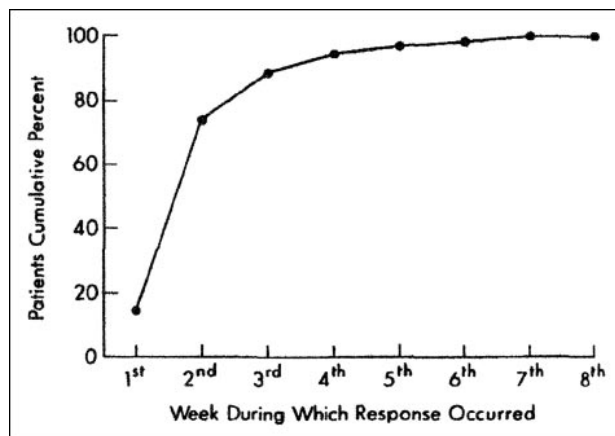


Figure 1. Cumulative distribution of time to response for initial responders. Note that approximately 95% of the children who eventually respond do so by 4 weeks of daily prednisone therapy. Reprinted with permission from *J Pediatr*. 1981;98:561–564.

Table 5. Indications for Renal Biopsy in Nephrotic Syndrome

At Time of Diagnosis:

Two or more of the following:

- Age >10 years
- Persistent or gross hematuria
- Hypertension
- Renal insufficiency
- Low C3 complement values

Subsequently:

- Persistent proteinuria (at the end of 4 weeks of daily prednisone therapy)

therapy, when the chance of subsequent response is approximately 5%. It is worth noting that microscopic hematuria is present during the first few weeks of illness in as many as one third of children who have MCNS. Persistence or recurrence of hematuria often is a sign of impending steroid resistance.

Clinical Features

The hallmark of nephrotic syndrome is heavy proteinuria, and the most common presenting sign is edema that becomes visible when fluid retention exceeds 3% to 5% of body weight. Usually, edema appears initially in areas of low tissue resistance (ie, periorbital, scrotal, and labial regions). Ultimately, it becomes generalized and can be massive (anasarca). Edema is characteristically dependent. In the morning, it is periorbital, frequently misinterpreted as being caused by an allergy, and later in the day is localized primarily to the lower extremities. Anorexia, irritability, fatigue, abdominal discomfort, and diarrhea are common symptoms. A respiratory tract infection preceding the onset of the disease by a few days often is reported, but its pathogenetic role is doubtful. A history of allergy is reported by as many as 50% of children who have MCNS.

Laboratory Findings

Plasma protein concentration is reduced markedly, due primarily to the loss of albumin in the urine; the serum albumin concentration usually is below 2.5 g/dL (25 g/L). The low concentration of albumin stimulates synthesis of lipids by the liver, resulting in high concentrations of cholesterol, triglycerides, and lipoproteins. Serum sodium may be decreased, due, in part, to hyperlipidemia and, in part, to the retention of water caused by hypovolemia and increased secretion of antidiuretic

hormone. The total calcium value may be low because of hypoalbuminemia, but the ionized calcium concentration is normal.

The concentration of protein in the urine can be estimated by the dipstick method. The strips are impregnated with tetrabromophenol blue, which reacts preferentially to albumin. The color change allows the reader to distinguish between a protein concentration of approximately 30 mg/dL (300 g/L) (1+), 100 mg/dL (1,000 g/L) (2+), 300 mg/dL (3,000 g/L) (3+), and 1,000 mg/dL (10,000 g/L) (4+). False-positive results may occur when the urine is alkaline (pH >7) or contains blood, pus, mucus, semen, or vaginal secretions. By this method, severity of proteinuria may be underestimated when the urine is diluted or overestimated when the urine is concentrated.

Patients who have a positive dipstick result should have a quantitative measurement of urinary protein excretion. Conventionally, this evaluation is performed on a 12- or 24-hour timed urine sample. An excretion of more than 50 mg/kg per day or 40 mg/m² per hour is considered indicative of nephrotic syndrome.

Accurate collections of urine are cumbersome, particularly in children, which explains the wide acceptance of the urine protein/creatinine ratio (UPr/Cr) as a reliable substitute. A strong correlation has been found between the UPr/Cr obtained in random specimens of urine and the 24-hour excretion of protein, corrected for body surface area (BSA). For children older than 2 years of age, a UPr/Cr of less than 0.2 is considered to be normal, a value of less than 0.5 is accepted as normal for children between 6 months and 2 years of age, and a value of more than 3.0 is consistent with nephrotic syndrome. Actual protein excretion (g/m² per day) can be calculated by the formula: $0.63 \times (\text{UPr/Cr})$. Due to circadian variations, the accuracy of the measurements can be increased by using a first-voided morning specimen.

Cause

The cause of MCNS remains unknown. A decrease in immune responsiveness or disorders affecting T-lymphocyte number or function has been postulated. (4) Also, there are reports of increased expression of interleukin-2 (IL-2) receptors on

T-lymphocytes; increases in IL-8, IL-13, insulin-like growth factor-1, transforming growth factor-beta, and interferon-gamma; abnormalities in nephrin expression or distribution; and the presence of a circulating “vascular permeability factor.” One such factor may be an active isoform of hemopexin, a plasma protein that can increase glomerular permeability by enhancing protease activity.

Recently, a group of investigators developed a humanized animal model of idiopathic nephrotic syndrome by injecting CD34⁺ stem cells or CD34⁻ peripheral blood mononuclear cells from patients afflicted with MCNS or FSGS into immunocompromised mice. (5) Only the injection of CD34⁺ stem cells induced albuminuria and effacement of the podocyte foot processes. This finding suggests that the cells responsible for the pathogenesis of MCNS, as well as FSGS, are likely immature cells undergoing differentiation into T cells.

Treatment and Course of MCNS

Prednisone is the drug of choice and should be started as soon as a presumptive diagnosis of primary nephrotic syndrome has been made, and infection, including tuberculosis, has been ruled out (Fig. 2). The treatment proposed by the ISKDC consisted of 60 mg/m² BSA per day, calculated on the basis of ideal weight for height (not to exceed 80 mg/day), divided in three doses. Daily administration was continued for 4 weeks, followed by 40 mg/m² BSA per day, given as a single dose in the morning, on alternate days, for an additional 4 weeks. Of

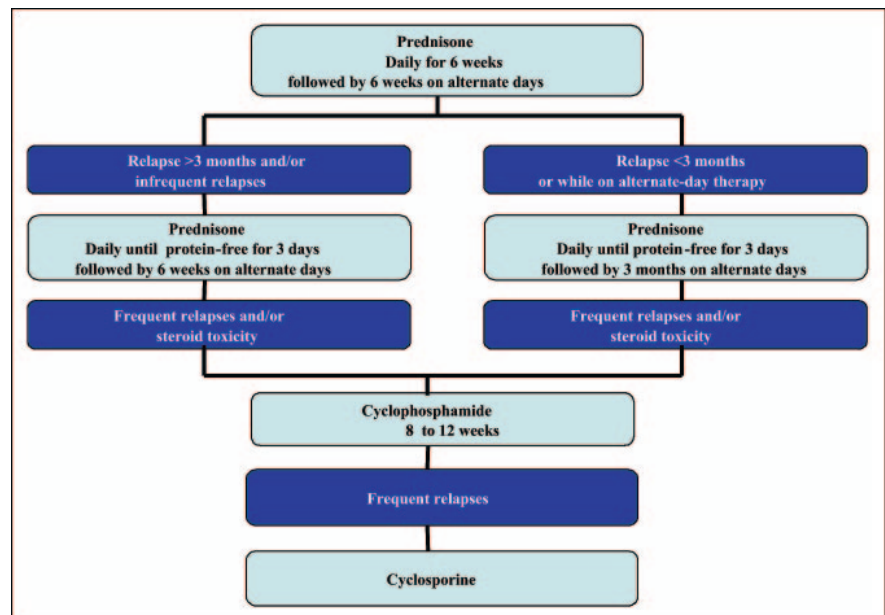


Figure 2. Treatment of minimal-change nephrotic syndrome.

the patients afflicted with MCNS, about 90% responded to steroids, and of those, about 60% relapsed. Subsequent studies of small numbers of children have revealed that similar rates of initial response can be achieved with twice-daily or even once-daily administration of prednisone. There are exceptions to this rule, however. A minority of children who fail to respond to a twice-daily regimen respond when given the daily prednisone in three divided doses.

In a retrospective analysis of 389 children included in the ISKDC studies who had MCNS, 80% were in remission at 8 years. Seventy-five percent of initial responders who remained in remission during the first 6 months after initial response either continued to be in remission or relapsed rarely. In contrast, initial “relapsers,” both frequent and infrequent, achieved a nonrelapsing course only after an average of 3 years. (6) Absence of hematuria at presentation, remission within 7 to 9 days from the start of treatment, and age older than 4 years have been reported to be predictive of few relapses. (7)

A prolonged initial treatment with prednisone (6 weeks of daily followed by 6 weeks of alternate-day administration) has been found to decrease the frequency of relapses. (8) In a Cochrane Review of the subject, the authors concluded that the higher the relapse rate with 2 months of initial treatment, the greater the effect of subsequent prolonged administration of prednisone. (9) Beginning with a relapse rate of 68% in children treated for 2 months, the relapse rate fell by an average of 7.5% with every 1-month increase in the length of treatment (approximately 30% at 6 months).

The treatment regimen used currently by most nephrologists consists of 6 weeks of daily prednisone, given in two divided doses, followed by 6 weeks of alternate-day prednisone given as a single dose in the morning. A relapse is treated with prednisone, 60 mg/m² BSA per day, given in two divided doses until the urine is protein-free for 3 consecutive days, followed by 40 mg/m² BSA per day, on alternate days, given as a single dose in the morning for 6 additional weeks, when the first relapse occurs more than 3 months after the initial response and for 12 additional weeks when the first relapse occurs within 3 months after the initial response.

Children who are frequent relapsers may benefit from an alkylating agent, such as cyclophosphamide (2 mg/kg per day), generally given for 8 to 12 weeks (Fig. 3). (10) A meta-analysis revealed that the relative risk of relapse in children who received this treatment is reduced by 60%. (11) The cumulative dose of cyclophosphamide should not exceed 200 mg/kg because of gonadal toxicity. Levamisole, chlorambucil, cyclosporine, and

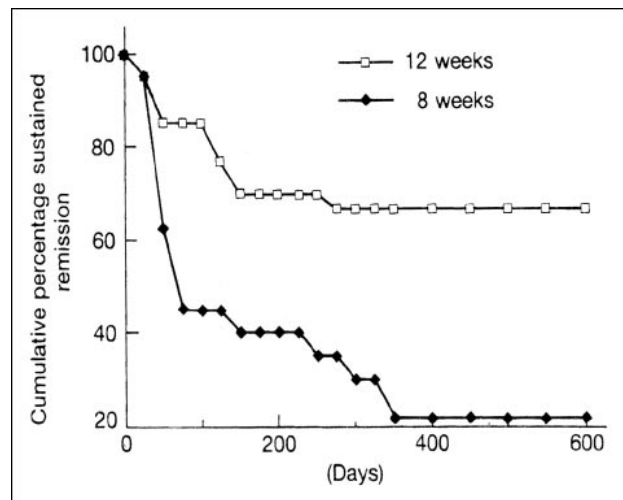


Figure 3. Actuarial remission rate after treatment with cyclophosphamide in steroid-dependent nephrotic syndrome. Reprinted with permission from *Arch Dis Child*. 1987;62:1102–1106.

mycophenolate-mofetil also have been found to reduce the frequency of relapses. In a number of uncontrolled studies, cyclosporine has been reported to reduce the incidence of relapses in 75% to 90% of patients who have steroid-dependent nephrotic syndrome. The drug has serious adverse effects (hypertension, hyperkalemia, hypertrichosis, gingival hyperplasia). Renal insufficiency, initially transitory, can become permanent due to interstitial fibrosis. Often, proteinuria recurs when the treatment is discontinued. (12) Cyclosporine administration requires careful monitoring of serum concentrations and should be undertaken only by experienced physicians. The frequency of relapses usually decreases with time, becoming rare at or after puberty. Nonetheless, as many as 52% of patients have been reported to have at least one relapse during adulthood. Pregnancy apparently is a predisposing factor. As long as the patient responds to steroid therapy, the risk of progression toward renal insufficiency remains negligible.

Steroid-resistant Nephrotic Syndrome

Steroid-resistant nephrotic syndrome may occur at birth or during the first postnatal year, but is more common after the age of 2 years. This group of patients represents no more than 10% of the entire population of children who have nephrotic syndrome, but their prognosis usually is bleak. Their renal function deteriorates, and eventually they become candidates for dialysis or renal transplantation.

Congenital Nephrotic Syndrome (CNS)

The name implies the presence of proteinuria at birth, leading to clinical symptoms shortly thereafter. Yet, an arbitrary limit of 3 months after birth is being used to separate the congenital from the infantile form of nephrotic syndrome.

The most common type of CNS is the Finnish type. CNF is an autosomal recessive disease, its incidence in Finland being 1 per 8,200 live births. However, patients who have CNF have been reported all over the world. In a subgroup of Mennonites from Lancaster, Pennsylvania, the incidence is 1 in 500, almost 20 times that encountered in Finland. In 1998, a gene (*NPHS1*) that codes for a protein (nephrin) located on podocytes was found to be mutated in CNF. (1) Soon thereafter, it became apparent that CNF also can be caused by mutations in *NPHS2*, which codes for another podocyte protein (podocin), and that mutations in *NPHS1* sometimes may cause mild, rather than severe, nephrotic syndrome.

The “typical” form of CNF is characterized by massive proteinuria that starts during fetal life. Elevated concentrations of alpha-fetoprotein in the amniotic fluid and normal fetal ultrasonographic findings serve to make a presumptive diagnosis of CNF. A definitive diagnosis requires genetic analysis of placental tissue or amniotic cells. Most affected children are born preterm, weighing a mean of 2,500 g. The amniotic fluid often is meconium stained, and the placenta is large. Edema and abdominal distention become evident soon after birth. The serum albumin concentration usually is below 1.0 g/dL (10 g/L). Albuminuria is massive and related directly to the concentration of albumin in the blood. Many other proteins, such as IgG, transferrin, antithrombin III, lipoprotein lipase, vitamin D-binding protein, and thyroid-binding protein, also are lost in the urine. These losses lead to metabolic disturbances, including lipid abnormalities that can produce atherosclerotic changes as early as the first postnatal year.

During the first months of extrauterine life, renal pathology is limited to slight-to-moderate mesangial cell proliferation by light microscopy and effacement of foot processes and thin glomerular basement membranes by electron microscopy. During the ensuing months, the renal tubules become dilated, mesangial hypercellularity increases, the Bowman capsule thickens, the interstitium becomes fibrotic, and glomeruli sclerose. Electron microscopy reveals the disappearance of the slit diaphragms.

Initial treatment aims to sustain a good nutritional state, control edema, and prevent complications such as infections and vascular thrombosis. Unilateral or bilateral nephrectomy (followed by peritoneal dialysis) often is

required to curtail the massive loss of protein. Successful treatment results in satisfactory growth and development and the chance for eventual kidney transplantation. In some patients, the nephrotic syndrome recurs, due to the development of antinephrin antibodies against the foreign antigens in the graft. Rare forms of CNS are those associated with diffuse mesangial sclerosis, specifically, the Denys-Drash, Galloway-Mowat, and Pierson syndromes. CNS also can be associated with infections such as syphilis, toxoplasmosis, cytomegalovirus, congenital rubella, and hepatitis B.

Focal-Segmental Glomerular Sclerosis

FSGS was identified half a century ago as a postmortem finding in 20 children who had nephrotic syndrome. The significance of this observation became apparent years later when the advent of renal biopsy allowed investigators to associate FSGS with steroid resistance. Initially, the disease consists of hyalinization or sclerosis of some glomeruli (focal) that involves only part of the glomerular tuft (segmental). The lesion appears in the juxtamedullary nephrons and extends to the cortex, resulting in progressive loss of renal function. The location of the lesion within the glomerulus may have prognostic significance. Peripheral lesions opposite the origin of the proximal tubule (“tip lesions”) appear to have a better prognosis than do hilar lesions, particularly those characterized by capillary collapse (collapsing glomerulopathy) that occur in immunocompromised patients. FSGS is fourfold more common and more aggressive in African Americans than in Caucasians or Asians. (2)

As in MCNS, the major signs of disease are edema and albuminuria. Hematuria is more frequent in FSGS than in MCNS, but the overlap diminishes its value as an element of diagnosis. Results of blood chemistries are indistinguishable from those in MCNS. The age at onset also is similar in the two conditions. Because of these similarities, FSGS cannot be diagnosed at presentation, and children commonly are started on standard prednisone therapy. Lack of response at 4 weeks prompts a renal biopsy, which often reveals the specific histologic lesion of FSGS. The lesion may be missed, however, if the tissue sample contains a small number of glomeruli or does not include juxtamedullary glomeruli, which are affected first. In addition, about 20% of children who have FSGS respond to steroid therapy and do not undergo a renal biopsy.

The relationship between MCNS and FSGS remains controversial. Some believe that these are two distinct entities; others believe that FSGS is a severe form of MCNS. The latter opinion is supported by the observa-

tion that some children who initially respond to steroids become steroid-resistant, with a renal biopsy revealing focal-segmental lesions.

FSGS is a heterogeneous condition, the histologic expression of a variety of diseases, including heroin-associated nephropathy, acquired immunodeficiency syndrome, multiple myeloma, Alport syndrome, reflux nephropathy, diabetic nephropathy, and obesity. Heterogeneity also applies to “idiopathic” FSGS. Some patients respond to steroid therapy; most do not. In some patients, disease progression is slow, reaching end stage in about 10 years; in others, it reaches that point in about 2 years. Moreover, in this latter group, the disease has a high likelihood of recurring in the transplanted kidney, probably due to the presence of a blood-circulating factor. Despite sustained efforts, no factor has been isolated. The heterogeneity of FSGS has been amplified by the recognition that some cases of FSGS are due to genetic abnormalities.

GENETIC FORMS OF FSGS. In recent years, impressive progress has been made in describing the molecular structure of the podocytes and the slit diaphragms that link them. Specifically, a number of proteins have been identified that work in concert to control the permeability of the glomerular membrane. Mutations in the genes that encode these proteins are associated with nephrotic syndrome and focal-segmental glomerular lesions. The impetus for this exploding field of research has been the discovery that lack of nephrin, a protein located at the slit-diaphragm, accounts for CNF. Table 1 summarizes the current state of knowledge. Genetic forms account for only a small percentage of FSGS. Genetic diagnosis, although commercially available, is expensive, is performed in only a few laboratories, and is justified only in isolated circumstances.

Despite the impressive progress made in identifying genetic types of FSGS, the cause of the disease still has not been identified in most patients. It has been proposed that genetic variants in two or more podocyte genes that alone do not produce disease may interact to cause FSGS. This concept, although enticing, is yet to be proved.

TREATMENT. The therapy for FSGS, regardless of variety, has been and continues to be a frustrating en-

deavor. It is reasonable to assert that no agent that could conceivably be of benefit to these patients has escaped clinical experimentation. Alas, no definitive evidence has emerged that any of these drugs is effective, although a few facts have been learned from these trials. Pulse methylprednisolone, hailed as being salutary for most children who have steroid-resistant nephrotic syndrome, has proven to be of minimal benefit. Alkylating agents such as cyclophosphamide also have been shown to have little therapeutic effect, but they continue to be used. In uncontrolled trials, cyclosporine has been reported to induce remission in 25% to 50% of patients who have steroid-resistant FSGS, but patients relapse promptly when the drug is discontinued and develop serious adverse effects if the treatment is sustained for long periods. A multicenter, prospective, controlled, randomized trial, sponsored by the National Institutes of Health, is in progress. Patients younger than 40 years of age who have biopsy-proven FSGS are assigned to treatment with either pulse steroids plus mycophenolate-mofetil or to

Infections are frequent and serious complications of nephrotic syndrome . . . The most common infection is peritonitis. . .

cyclosporine. The results of this therapeutic trial will not be known for several years.

Recurrence of disease in transplanted kidneys is a major problem; it has been reported to occur in as many as 50% of children who have FSGS. Being older than 6 years of age at onset and progression to end-stage renal disease in fewer than 3 years are considered risk factors. For most affected children, proteinuria develops within hours after transplantation, although it may start as late as 3 months later. High-dose cyclosporine, plasmapheresis, or a combination of both is associated with partial or total remission in a minority of cases. The outcome of the treatment is unpredictable.

Membranous Nephropathy

MN was identified initially postmortem as a diffuse, irregular thickening of the glomerular basement membranes in the absence of any inflammatory changes. With the introduction of acid-silver-methenamine stain and electron microscopy, it became evident that the distor-

tion of the basement membranes is due to the presence of blobs of silver-negative, electron-dense deposits. The deposits are located exclusively in the subepithelial area and are flanked by silver-positive tissue, giving the appearance of spikes. MN is very rare in children and can manifest at any age. It presents as either asymptomatic proteinuria or nephrotic syndrome. Microscopic hematuria and hypertension are rare. No clinical or laboratory findings allow a positive identification; the diagnosis rests ultimately on the specific histologic findings.

The disease can be either primary or due to a variety of conditions, including infections (hepatitis B, malaria, syphilis), autoimmune diseases (SLE, Crohn disease), drugs (penicillamine), tumors (Wilms, neuroblastoma), and other disorders. The pathogenesis of MN has not been determined precisely, although evidence points toward binding of an antibody to an in situ glomerular basement membrane antigen. In several cases of neonatal MN, a podocyte antigen, neutral-endopeptidase, (13) served as the pathogen. Antibodies to this protein originated in pregnant women who lacked the neutral endopeptidase epitop due to a mutational deletion. No similar findings have been reported in older patients.

The course of the disease is variable. Spontaneous remissions occur in 25% to 50% of children, whereas 25% to 30% develop renal insufficiency. Treatment with steroids and immunosuppressive drugs is common, although the results have been discouraging.

Complications of Nephrotic Syndrome

Some patients exhibit signs of acute renal failure (ie, reduction in glomerular filtration rate and oliguria). These signs usually are reversed when the intravascular volume is expanded by infusion of salt-poor human albumin and diuresis is induced by furosemide or other diuretic drugs. Rarely, acute renal failure can be caused by bilateral renal vein thrombosis. The diagnosis is made by ultrasonography. Thromboembolic complications also can affect the lungs, the brain, and the peripheral vessels. The overall incidence of thromboembolic events is about 3%. Such events are caused by loss of antithrombin III and protein S in the urine as well as an increase in fibrinogen concentration, leading to a hypercoagulable state.

The antiphospholipid syndrome also has been incriminated as a cause of thromboembolic complications in some patients who have nephrotic syndrome. This disorder is characterized by persistently elevated concentrations of antibodies directed against membrane anionic phospholipids (eg, anticardiolipin antibody, antiphosphatidylserine) or their associated plasma proteins, pre-

dominantly beta-2 glycoprotein I (apolipoprotein H). A circulating anticoagulant also may be present. The mechanism of thrombosis in this syndrome has not yet been defined. Emerging evidence from murine models suggests that antiphospholipid-mediated complement activation may be the primary event. Irrespective of cause or pathogenesis, the first line of treatment is low-molecular weight heparin. If the thrombosis extends, thrombolytic drugs, such as tissue plasminogen activator, followed by warfarin should be considered. Warfarin should be discontinued as soon as the nephrotic syndrome resolves.

Infections are frequent and serious complications of nephrotic syndrome. Urine loss of factor B (which contributes to opsonization of bacteria), a decrease in IgG synthesis, and impaired T-cell function contribute to the susceptibility to infection. The most common infection is peritonitis, which used to be due primarily to *Streptococcus pneumoniae*. Vaccination has reduced infections with *S pneumoniae* substantially and increased the relative frequency of gram-negative organisms. There also has been an increase in penicillin-resistant *S pneumoniae*.

A high degree of suspicion must be maintained when caring for patients who have ascites. Fever and chills occur in as many as 80% of patients who have peritonitis. Abdominal pain or discomfort is found in as many as 70% of patients and often is accompanied by ileus or diarrhea. Peritoneal fluid must be analyzed for any patient in whom peritonitis is considered. An ascitic fluid neutrophil count of more than 500 cells/mcL is the single best predictor of infection, with a sensitivity of 86% and specificity of 98%. Lowering the ascitic fluid neutrophil count to more than 250 cells/mcL results in an increased sensitivity (93%) but a lower specificity (94%). Notably, steroids do not mask the signs and symptoms of peritonitis. (14)

A combination of an aminoglycoside and ampicillin provides empiric coverage of more than 90% of cases of peritonitis caused by gram-negative aerobes or gram-positive cocci. The third-generation cephalosporin cefotaxime is as efficacious and is not nephrotoxic but does not treat enterococci. Subsequently, antibiotic therapy should be guided by the results of ascitic fluid cultures and sensitivities.

Cellulitis, meningitis, and pneumonitis also may occur in patients who have nephrotic syndrome. Anasarca and pulmonary edema are preventable complications of nephrotic syndrome and reflect massive retention of sodium and water, consequent to the loss of albumin in the urine and its leakage into the extravascular compartment. Diuretic drugs and salt-poor albumin infusions are only

partially effective. The primary goal of therapy should be diminution of protein loss. Stunting of growth, a complication of prolonged steroid administration, is well recognized. Thirty-four patients who had a frequently relapsing course and a mean age of 8.0 years at onset were found to have a mean height 2.5 cm below the target height, when evaluated 13 years later. (15) Growth rate should be monitored closely in frequent relapsers or steroid-dependent children, and an alternative therapy (cyclophosphamide, mycophenolate-mofetil, cyclosporine) should be considered as soon as the growth curve plateaus.

Reduced mineral bone density, a recently recognized complication of MCNS, is due to the prolonged administration of steroids and, possibly, to vitamin D deficiency. In a randomized, controlled study of 40 children who had MCNS, daily administration of 400 IU of vitamin D and 1 g of calcium diminished, but did not end, the decrease in bone mineral density.

Ancillary Therapy of Nephrotic Syndrome

Edema in nephrotic syndrome requires treatment only when it is associated with severe ascites, peritonitis, respiratory distress, or heart failure. The first line of therapy is diuretic drugs. Commonly used are loop diuretics (furosemide, ethacrynic acid), which block reabsorption of sodium in the loop of Henle, and thiazide diuretics (hydrochlorothiazide), which block reabsorption of sodium in the distal tubule. For patients who fail to respond to diuretics, concomitant administration of salt-poor albumin (0.5 to 1 g/kg body weight up to 25 g, in a 25% solution administered intravenously over 30 to 60 minutes) may induce diuresis. This treatment appears to be particularly effective in children who have very low serum albumin concentrations (<1.5 g/dL [15 g/L]) and in those who have clinical signs of intravascular volume contraction. Aggressive administration of diuretic drugs may induce hypovolemia and secondary renal failure, thromboembolism, or electrolyte disturbances. Hypovolemia can be prevented or treated by administration of salt-poor albumin.

Approximately 20 years ago, it was noticed that angiotensin II inhibitors diminished proteinuria, independently of their effect on blood pressure and glomerular filtration rate. As a result, ACE inhibitors and angiotensin receptor blockers, given alone or in combination, have become important components of the antiproteinuric therapy. Twelve weeks of treatment were reported to reduce proteinuria by about 1 g/24 hours. Recently, it has been found that ACE inhibitors prevent loss of podocytes and preserve nephrin expression; they also

may slow progression of renal disease. A protective effect on renal function also was seen with angiotensin receptor blockers.

Hyperlipidemia is one of the primary features of the nephrotic syndrome that may persist well beyond remission. Several studies have revealed premature coronary atherosclerosis and increased incidence of myocardial infarction in patients who have nephrotic syndrome. Hyperlipidemia also may contribute to progression of renal disease. These observations have prompted many physicians to use statins in patients who have had persistent hyperlipidemia. Statins also have been found to slow the progression of chronic renal disease, albeit to a trivial extent. These effects may be due to improvement of endothelial function, systemic or intrarenal anti-inflammatory actions, amelioration of oxidative stress, and inhibition of macrophage recruitment and function.

Vaccination of children who have nephrotic syndrome has been found to be generally effective. Antibody responses to pneumococcal, influenza, varicella, and hepatitis vaccines have been adequate, and the adverse effects have not been found to be different from those reported in the general population. However, pneumococcal and hepatitis antibody concentrations were reported to decline faster in children who had nephrotic syndrome than in the general population. The Committee on Infectious Diseases of the American Academy of Pediatrics recommends vaccination with the conjugated pneumococcal vaccine. The state of immunity to varicella should be assessed for patients who have not been vaccinated, and treatment with acyclovir should be started as soon as an at-risk patient is exposed to the virus.

Retention of sodium is paramount to water retention and the development of edema. Thus, a low-sodium diet is warranted, although fluid intake does not need to be restricted as long as sodium intake is limited. Prolonged loss of proteins in the urine may compromise the nutritional status of the children and must be prevented by an adequate diet and, when necessary, the addition of high-protein products. Vitamin D and calcium supplementation also are advisable.

Summary and Conclusions

Nephrotic syndrome encompasses a diverse group of conditions that share the common denominator of massive loss of protein in the urine. Progress in identifying the cause and pathogenesis of each of these conditions has been slow. The current identification of various forms of nephrotic syndrome is based primarily on histologic findings, which are not always pathognomonic.

Treatment has and still depends on drugs that lack specificity and have numerous, often serious, adverse effects.

The following conclusions are worth remembering:

- Most children who have nephrotic syndrome have MCNS, which is responsive to prednisone therapy.
- Response to steroid therapy is the best prognostic indicator.
- Most (~60%) of children who have MCNS relapse, some of them frequently. Cyclophosphamide and cyclosporine decrease the incidence of relapses.
- Compelling evidence suggests that renal biopsy should be performed at onset only in children who, in addition to proteinuria, have macroscopic hematuria, hypertension, persistent renal insufficiency, or low C3 complement values. Another indication is failure to respond to steroid therapy (proteinuria still present at the end of 4 weeks of daily prednisone therapy).
- Most children who have nephrotic syndrome and fail to respond to steroids have FSGS. Most alkylating agents are ineffective. Cyclosporine has been reported, in uncontrolled studies, to induce remission in 20% to 50% of patients who failed to respond to steroids. The drug requires monitoring of serum values and has serious adverse effects. Proteinuria recurs in most patients as soon as the treatment is discontinued.
- Several genetic forms of FSGS, due to mutations that encode proteins at the level of the podocytes, have been identified. They account for a small minority of patients who have nephrotic syndrome, and none responds to treatment.
- Dialysis and transplantation have improved the long-term prognosis of patients who reach end-stage renal disease, even infants who have CNS.
- Some glomerulopathies, such as FSGS, MPGN, and possibly CNS, may recur in renal transplants. Treatment with immunosuppressive agents and plasmapheresis is effective in about 30% of such patients.

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Suggested Reading

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- Shankland SJ. The podocyte's response to injury: role of proteinuria in glomerulosclerosis. *Kidney Int.* 2006;69:2131–2147

PIR Quiz

Quiz also available online at www.pedsinreview.aappublications.org.

6. A 4-year-old boy presents with swelling of the face and extremities of 2 days' duration. Physical examination reveals an otherwise happy child who has swelling of the face and pitting edema of all extremities. Vital signs and the rest of the physical examination findings are normal. Urinalysis shows 4+ proteinuria and 5 red blood cells per high-power field. Of the following, the *most* likely abnormality on histologic examination of this boy's kidney is:
 - A. Deposition of immunoglobulin A in mesangium.
 - B. Diffuse thickening of glomerular capillary walls.
 - C. Fusion of epithelial foot processes only.
 - D. Mesangial cell proliferation and thickening of Bowman capsule.
 - E. Scar tissue in segments of some glomeruli.

7. A 4-year-old boy presents with swelling of the face and extremities of 2 days' duration. Physical examination reveals an otherwise happy child who has swelling of the face and pitting edema of all extremities. Vital signs and the rest of the physical examination findings are normal. Urinalysis shows 4+ proteinuria and 5 red blood cells per high-power field. Of the following, the *best* indicator of good outcome for this child is:
 - A. Normal C3 complement value.
 - B. Normal serum creatinine concentration.
 - C. Resolution of symptoms with prednisone treatment.
 - D. Serum cholesterol less than 500 mg/dL (13.0 mmol/L).
 - E. Urine protein:creatinine ratio less than 5.

8. You are treating a 9-year-old girl who has nephrotic syndrome with prednisone. Which of the following is the *strongest* indication for performing renal biopsy?
 - A. Lack of response to therapy after 1 week.
 - B. Microscopic hematuria showing more than 5 red blood cells per high-power field in urine.
 - C. Reduced serum concentration of C3 complement.
 - D. Serum albumin less than 1.5 g/dL (15 g/L).
 - E. Urine protein:creatinine ratio of 1 at presentation.

9. A 6-year-old girl is admitted for swelling of her face and extremities. Findings on her physical examination and vital signs are normal except for generalized anasarca. Urinalysis shows 4+ protein with no casts or red blood cells. Serum albumin is 1.3 g/dL (13 g/L), cholesterol is 550 mg/dL (14.2 mmol/L), and creatinine is 0.4 mg/dL (35.4 μ mol/L). This patient is at *greatest* risk for:
 - A. Centrilobular hepatic necrosis.
 - B. Cerebral edema.
 - C. Congestive heart failure.
 - D. Myoglobinuric renal failure.
 - E. Peritonitis.

The Nephrotic Syndrome
Roberto Gordillo and Adrian Spitzer
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thology typically demonstrates a mixture of reactive cells in addition to Reed-Sternberg cells. Although not pathognomonic, the Reed-Sternberg cell or one of its variants almost always is identified in patients who have HD.

In the past, staging laparotomy with splenectomy was performed routinely in patients who had HD. However, splenectomy placed patients at risk for overwhelming infection, with a mortality rate of 5% in affected children. Although infectious complications following splenectomy have decreased with newer vaccines and antibacterial prophylaxis, staging splenectomy no longer is performed routinely because studies have not shown improvement in cancer survival as a result of staging.

Management

Cure rates for pediatric HD when multiagent chemotherapy and radiation therapy are used are among the highest in pediatric oncology. Current clinical research is focused on decreasing drug and radiation doses to limit the late effects of treatment, including infertility, cardiac disease, and secondary malignancy.

This patient was started on multiagent chemotherapy, but his response was less brisk than anticipated. He currently is being treated on a salvage chemotherapy regimen. Treatment will include radiation therapy to known sites of disease.

Lessons for the Clinician

- Hodgkin disease can have a variety of presentations. A common pre-

sentation is lymphadenopathy in the supraclavicular or cervical areas, but sometimes no lymphadenopathy is appreciated and the entire physical examination is unrevealing.

- The patient's history of the present illness and recent past medical history can provide important clues in making the diagnosis.
- Whenever Hodgkin disease is considered in the differential diagnosis, a chest radiograph should be considered.

(J.L. Becton, Jr, MD, Colleen McDonough, MD, Medical College of Georgia, Augusta, Ga.)

To view Suggested Reading lists for these cases, visit pedsinreview.aappublications.org and click on Index of Suspicion.

Clarification

There is an incorrect protein assessment conversion in the first full paragraph on page 98 of the article "The Nephrotic Syndrome" in the March issue (*Pediatr Rev.* 2009;30:94–105). The units of measure for the protein concentrations in the parentheses should be mg/L rather than the g/L that was printed.



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