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Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children

Author:
Patrick Niaudet, MD
Section Editor:
Tej K Mattoo, MD, DCH, FRCP
Deputy Editor:
Melanie S Kim, MD
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INTRODUCTION

The nephrotic syndrome is caused by renal diseases that increase the permeability across the glomerular filtration barrier. It is classically characterized by four clinical features, but the first two are used diagnostically because the last two may not be seen in all patients:

- Nephrotic range proteinuria − Urinary protein excretion greater than 50 mg/kg per day
- Hypoalbuminemia − Serum albumin concentration less than 3 g/dL (30 g/L)
- Edema
- Hyperlipidemia

The etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children are reviewed here. The complications and treatment of idiopathic childhood nephrotic syndrome and specific renal diseases that present as nephrotic syndrome in children are discussed separately. (See "Complications of nephrotic syndrome in children" and "Treatment of idiopathic nephrotic syndrome in children" and "Etiology, clinical features, and diagnosis of minimal change disease in adults" and "Congenital and infantile nephrotic syndrome" and "Focal segmental glomerulosclerosis: Epidemiology, classification, clinical features, and diagnosis".)

PATHOGENESIS

Two issues are important in the pathogenesis of nephrotic syndrome: the mechanisms of glomerular injury and proteinuria.

Mechanisms of glomerular injury — A variety of different, disease-specific mechanisms have been described in the nephrotic syndrome:

- Circulating factors in minimal change disease (MCD) and primary focal segmental glomerulosclerosis (FSGS). (See 'Idiopathic nephrotic syndrome'below.)
- Circulating immune factors in disorders such as membranoproliferative glomerulonephritis, poststreptococcal glomerulonephritis, and lupus nephritis. (See "Mechanisms of immune injury of the glomerulus".)
- Mutations in podocyte or slit diaphragm proteins (eg, CD2AP, podocin, and nephrin) in inherited forms of congenital, infantile, or glucocorticoid-resistant nephrotic syndrome. (See "Congenital and infantile nephrotic syndrome" and "Steroid-resistant idiopathic nephrotic syndrome in children: Etiology", section on 'Genetic mutations'.)

Mechanisms of proteinuria — The mechanisms of proteinuria in patients with nephrotic syndrome are discussed in detail elsewhere, but will be briefly reviewed here. (See "Assessment of urinary protein excretion and evaluation of isolated non-nephrotic proteinuria in adults", section on 'Glomerular proteinuria'.)

The proteinuria in glomerular disease is due to increased filtration of macromolecules (such as albumin) across the glomerular capillary wall. The latter consists of three components: the fenestrated endothelial cell, the glomerular basement membrane (GBM), and the epithelial cell foot processes. The pores between the foot processes are closed by a thin membrane called the slit diaphragm (picture 1).

The filtration of macromolecules across the glomerular capillary wall is normally restricted by two mechanisms: charge-selectivity and size-selectivity. The endothelial cells and the GBM have a net negative charge due to polyanions such as heparan sulfate proteoglycans. This creates a charge barrier to the filtration of large anions such as albumin. In comparison, circulating immunoglobulin G (IgG) is predominantly neutral or cationic, and its filtration is not limited by charge.

In MCD, the most common cause of nephrotic syndrome in children, there is a loss of anionic charge that is not accompanied by any structural damage or change to the glomerular filtration unit observed by light microscopy. However, electron microscopy demonstrates epithelial podocyte effacement (picture 2). (See "Etiology, clinical features, and diagnosis of minimal change disease in adults", section on 'Pathogenesis'.)

The glomerular capillary wall is size-selective, having functional pores of an approximate radius of 40 to 45 A (the radius of albumin is roughly 36 A). These pores appear to be located throughout the GBM and across the GBM at the slit diaphragms between the adjacent epithelial cell foot processes. In comparison, the width of the endothelial cell fenestrae is much larger (375 to 400 A); as a result, the endothelial cell is not part of the size barrier to macromolecule filtration.

In glomerular diseases other than MCD, structural injury seen by light microscopy results in an increase in the number of large pores in the GBM (figure 1). This structural damage allows movement of normally restricted proteins of varying sizes (including large neutral proteins, such as IgG) across the filtration barrier.

CLASSIFICATION AND ETIOLOGY

In this discussion, children with nephrotic syndrome are classified based upon whether or not there are signs of systemic disease. We use the following classification system:

- Primary nephrotic syndrome, which refers to nephrotic syndrome in the absence of an identifiable systemic disease. Within this category are patients with idiopathic nephrotic syndrome, who have no glomerular inflammation on renal biopsy, and patients with primary glomerulonephritis, who have an active sediment and glomerular inflammation on renal biopsy.
- Secondary nephrotic syndrome, which refers to nephrotic syndrome in the presence of an identifiable systemic disease. (See 'Secondary nephrotic syndrome' below.)
- Congenital and infantile nephrotic syndrome, which occur in children less than one year of age and can be either secondary (mostly due to infection) or primary. Two-thirds of nephrotic syndrome cases that occur during the first year of life and as many as 85 percent of cases that occur during the first three months of life have a genetic basis and a poor outcome [1]. These disorders are discussed separately. (See "Congenital and infantile nephrotic syndrome".)

Primary nephrotic syndrome — Primary nephrotic syndrome is defined as nephrotic syndrome in the absence of systemic disease, with a reported incidence of 1.5 per 100,000 children per year [2]. Within this category are two subgroups:

- Disorders without glomerular inflammation on renal biopsy. Included in this group are idiopathic nephrotic syndrome and some cases of membranous nephropathy, which are discussed elsewhere. (See "Membranous nephropathy: Epidemiology, pathogenesis, and etiology".)
- Nephritic disorders associated with an active urine sediment (red cells and cellular casts) and the presence of glomerular inflammation on renal biopsy. Included in this group are membranoproliferative glomerulonephritis and immunoglobulin A (IgA) nephropathy, which are discussed separately. (See "Clinical presentation, classification, and causes of membranoproliferative glomerulonephritis" and "Clinical presentation and diagnosis of IgA nephropathy" and "Glomerular disease: Evaluation in children", section on 'Glomerulonephritis'.)

Idiopathic nephrotic syndrome — Idiopathic nephrotic syndrome is the most common form of childhood nephrotic syndrome, representing more than 90 percent of cases between 1 and 10 years of age and 50 percent after 10 years of age [3]. Idiopathic nephrotic syndrome is defined by the association of a nephrotic syndrome with renal biopsy findings of diffuse foot process effacement on electron microscopy and minimal changes (called minimal change disease [MCD]), focal segmental glomerulosclerosis (FSGS), or mesangial proliferation on light microscopy. It is unclear whether these three light microscopic patterns represent separate disorders or are a spectrum of a single disease process [4]. (See "Etiology, clinical features, and diagnosis of minimal change disease in adults" and "Focal segmental glomerulosclerosis: Epidemiology, classification, clinical features, and diagnosis" and "Minimal change variants: Mesangial proliferation; IgM nephropathy; C1q nephropathy".)

Most patients have histologic findings of MCD. The vast majority of patients with MCD (>90 percent) respond to steroid therapy [5].

MCD can be clinically differentiated from other causes of nephrotic syndrome. This was illustrated in a classic study from the International Study of Kidney Disease in Children (ISKDC) of 521 children (age range 12 weeks to 16 years of age) who presented with primary nephrotic syndrome. The study was conducted in 24 centers in North America, Europe, and Asia between 1967 and 1974 [3]. Renal biopsies were obtained in all children.

Multivariate analysis demonstrated that clinical findings at presentation accurately differentiated children with MCD from those with other glomerular pathology [3]. These findings included:

- Age younger than six years of age
- Absence of hypertension
- Absence of hematuria by Addis count
- Normal complement levels
- Normal renal function

One exception to the age criterion is onset of nephrotic syndrome in the first year of life, particularly the first three months of life, which is much more likely to be due to a gene mutation and to be resistant to glucocorticoids [1].

Based upon these observations, an initial trial of steroid therapy is generally administered to children who are likely to have MCD based upon clinical diagnosis, thereby avoiding renal biopsy. (See 'Minimal change disease' below.)

Patients with idiopathic nephrotic syndrome are further classified based upon their response to empiric steroid therapy. (See "Treatment of idiopathic nephrotic syndrome in children".)

- Steroid-responsive nephrotic syndrome − The majority of children with idiopathic nephrotic syndrome are steroid-responsive (also referred to as steroid-sensitive nephrotic syndrome). In these patients, the most likely histologic lesion is MCD, although some patients with FSGS will also respond to steroid therapy [5]. Patients who are steroid-responsive have a favorable long-term outcome with a very low risk of chronic renal disease.
- Steroid-resistant nephrotic syndrome − Approximately 20 percent of all children with idiopathic nephrotic syndrome will not respond to steroid therapy. The response rate is better in younger children, who are much more likely to have MCD. In an ISKDC study, only approximately 10 percent of children less than 10 years of age failed to respond to steroids [5]. Patients with idiopathic steroid-resistant nephrotic syndrome have a worse prognosis, as renal survival rate in Caucasian children is approximately 50 percent at 10 years and even worse in children with African or Hispanic ethnicity [5-7].

Some children with steroid-resistant nephrotic syndrome have genetic mutations of podocyte proteins, including *NPHS2*, *NPHS1*, and *WT1* genes. (See "Steroid-resistant idiopathic nephrotic syndrome in children: Etiology", section on 'Genetic mutations'.)

Secondary nephrotic syndrome — Secondary nephrotic syndrome is defined as nephrotic syndrome associated with systemic diseases or is secondary to another process that causes glomerular injury. Within this category are the same two subgroups as in primary nephrotic syndrome:

- Disorders without glomerular inflammation on renal biopsy. Included in this group are some cases of membranous nephropathy (eg, due to lupus, chronic hepatitis B infection), secondary FSGS due to nephron loss resulting from renal scarring or hypoplasia, and, rarely, disorders such as amyloidosis. (See "Membranous nephropathy: Epidemiology, pathogenesis, and etiology" and "Focal segmental glomerulosclerosis: Pathogenesis", section on 'Pathogenesis of secondary FSGS'.)
- Nephritic disorders associated with an active urine sediment (red cells and cellular casts) and the presence of glomerular inflammation on renal biopsy. A variety of disorders are included in this group.
  - Postinfectious glomerulonephritis and infective endocarditis. (See "Poststreptococcal glomerulonephritis" and "Kidney disease in the setting of infective endocarditis or an infected ventriculoatrial shunt".)
  - Systemic lupus erythematosus. (See "Diagnosis and classification of renal disease in systemic lupus erythematosus".)
  - Vasculitides, such as IgA vasculitis (Henoch-Schönlein purpura), and, rarely, in granulomatosis with polyangiitis (formerly referred to as Wegener's granulomatosis) and microscopic polyangiitis. (See "IgA vasculitis (Henoch-Schönlein purpura): Renal manifestations" and "Granulomatosis with polyangiitis and microscopic polyangiitis: Clinical manifestations and diagnosis".)
  - Other causes include sickle cell disease, which is usually associated with secondary FSGS, Alport syndrome, and hemolytic uremic syndrome. (See "Renal manifestations of sickle cell disease" and "Genetics, pathogenesis, and pathology of Alport syndrome (hereditary nephritis)".)

EPIDEMIOLOGY

The estimated incidence of pediatric nephrotic syndrome is 2 per 100,000 children per year [2,8]. Primary nephrotic syndrome is more common in younger children, particularly in those less than six years of age [2,3,8]. There is a male predominance, with reported ratios of boys to girls of 2 to 1.

Minimal change disease (MCD) is the most commonly seen diagnosis of childhood nephrotic syndrome based on histopathology. In the previously mentioned International Study of Kidney Disease in Children (ISKDC) study of 521 children who presented with idiopathic nephrotic syndrome without systemic disease between 1967 and 1974, the following findings were made based upon renal biopsy [3]:

- MCD − 77 percent
- Membranoproliferative glomerulonephritis (MPGN) − 8 percent
- Focal segmental glomerulosclerosis (FSGS) − 7 percent
- Proliferative glomerulonephritis − 2 percent
- Mesangial proliferation − 2 percent
- Focal and global glomerulosclerosis − 2 percent
- Membranous glomerulonephropathy − 2 percent

Eighty percent of patients with MCD and 50 percent of patients with FSGS presented before six years of age. In contrast, none of the 39 patients with MPGN presented before six years of age.

Subsequent studies have demonstrated an increasing prevalence of FSGS [9,10]. Whether this is due to a true increase in prevalence or is a result of improved detection of the histologic changes consistent with FSGS on renal biopsy is unknown. Since the diagnosis of FSGS is made by the detection of one or more glomeruli with segmental glomerulosclerosis, one cannot be certain that a patient with an initial diagnosis of MCD does not actually have FSGS that was missed because of sampling error.

There is an increased incidence of nephrotic syndrome in family members when compared with the general population [11,12]. In affected siblings, nephrotic syndrome usually presents at the same age with the same histopathology and outcome [12].

CLINICAL MANIFESTATIONS

Nephrotic syndrome in children is characterized by general edema. Elevated blood pressure and hematuria are less common findings in children with minimal change disease than in children with focal segmental glomerulosclerosis or secondary causes of nephrotic syndrome.

Edema — Childhood idiopathic nephrotic syndrome generally presents with edema and often occurs after an inciting event, such as an upper respiratory infection or an insect bite. Edema increases gradually and becomes detectable when fluid retention exceeds 3 to 5 percent of body weight. Typically, periorbital edema is noted first and is often misdiagnosed as a manifestation of allergy. The edema is gravity dependent, and thus, over the day, periorbital edema decreases while edema of the lower extremities increases. In the reclining position, edema localizes to the back and sacral area. Other dependent areas that can become edematous include the scrotum, penis, or labia. The affected areas are nonerythematous, soft, and pitting.

Some patients develop anasarca (ie, generalized and massive edema) with marked peripheral edema, abdominal distension resulting from ascites, marked scrotal or vulvar edema, and severe periorbital edema resulting in swollen shut eyelids.

Despite the marked increase in extracellular fluid volume, some children with nephrotic syndrome, primarily those with minimal change disease (MCD), present with or develop signs of a decrease in effective circulating volume, such as tachycardia, peripheral vasoconstriction, oliguria, decreased glomerular filtration rate (GFR), and elevation of plasma renin, aldosterone, and norepinephrine [13]. In such children, a further insult such as diuretic therapy, sepsis, or diarrhea can lead to hypotension and, rarely, shock [14]. (See "Symptomatic management of nephrotic syndrome in children", section on 'Edema'.)

A variety of other manifestations can occur. (See "Complications of nephrotic syndrome in children".)

- Umbilical or inguinal hernias.
- Abdominal pain due to rapid fluid accumulation or peritonitis.
- Dyspnea, which is most often due to respiratory compromise from pleural effusions or marked ascites. Infrequently, respiratory symptoms may be due to pneumonia or, rarely, pulmonary embolus due to the hypercoagulable state associated with the nephrotic syndrome.
- Nonspecific complaints, including headache, irritability, malaise, and fatigue are common at presentation.

Elevated blood pressure — The likelihood of elevated blood pressure varies with the underlying cause of nephrotic syndrome [3]. Hypertension is common in patients with glomerulonephritis, but is infrequent in patients with minimal change disease. For patients with glomerulonephritis, hypertensive encephalopathy is an uncommon but serious complication. (See "Glomerular disease: Evaluation in children", section on 'Clinical features' and "Approach to hypertensive emergencies and urgencies in children".)

Hematuria — Gross hematuria is most often seen in patients with glomerulonephritis (eg, postinfectious glomerulonephritis or membranoproliferative glomerulonephritis). In contrast, gross hematuria is rare in idiopathic nephrotic syndrome, although microscopic hematuria is seen in 20 percent of cases [3]. (See 'Urinalysis' below.)

Associated complications — Uncommon but serious complications of nephrotic syndrome include:

- Serious bacterial and viral infection due to immunologic impairment (See "Complications of nephrotic syndrome in children", section on 'Infection'.)
- Thromboembolism due to hypercoagulability (See "Complications of nephrotic syndrome in children", section on 'Thromboembolism'.)

DIAGNOSIS

Although edema is generally the presenting sign of nephrotic syndrome, the diagnosis is confirmed by the presence of both nephrotic range proteinuria and hypoalbuminemia.

- Urinary protein excretion greater than 50 mg/kg per day (See 'Urine protein excretion' below.)
- Hypoalbuminemia (See 'Serum albumin' below.)

Minimal change disease — A presumptive diagnosis of minimal change disease (MCD), the most common cause of pediatric NS, is made based on the following additional clinical findings [3] (see 'Idiopathic nephrotic syndrome' above):

- Age younger than six years of age
- Absence of hypertension
- Absence of hematuria
- Normal complement levels
- Normal renal function

DIAGNOSTIC EVALUATION

Clinical and laboratory findings are used to confirm the diagnosis of NS and can also be used to diagnose specific underlying causes of nephrotic syndrome. In particular, clinical findings are highly predictive of minimal change disease (MCD) [3]. In almost all patients with MCD, steroid therapy is initiated without renal biopsy based on a clinical diagnosis.

Our approach is consistent with the following initial evaluation of nephrotic syndrome developed by the Children's Nephrotic Syndrome Consensus Conference [15].

- Urinalysis
- First morning void to measure urinary protein to creatinine ratio
- Blood tests, including electrolytes, creatinine, blood urea nitrogen, cholesterol, albumin, and C3
- Other blood tests include antinuclear antibody level for patients ≥10 years of age or with signs of systemic lupus erythematosus, and serology for hepatitis B, C, and human immunodeficiency virus (HIV) in high-risk populations
- Renal biopsy for children ≥12 years of age

Urine tests

Urine protein excretion — Nephrotic range proteinuria in children is defined as urinary protein excretion greater than 50 mg/kg per day or 40 mg/m^2 per hour. Quantitative measurement of protein excretion is based upon a timed 24-hour urine collection.

However, it is difficult to obtain accurately timed urine collections in young children. An alternative method of quantitative assessment of urine protein excretion is measurement of the total protein/creatinine ratio on a spot urine

sample (calculator 1). The ratio that is indicative of nephrotic range proteinuria is greater than 3 mg protein/mg creatinine (300 mg protein/mmol creatinine). (See "Evaluation of proteinuria in children", section on 'Quantitative assessment'.)

Urinalysis — The urinary dipstick measures albumin concentration via a colorimetric reaction between albumin and tetrabromophenol blue. It measures protein concentration rather than the rate of protein excretion and, therefore, cannot be used to make the diagnosis of nephrotic syndrome. However, in most patients with nephrotic syndrome, the urinary dipstick demonstrates a high albumin concentration (3+ to 4+, 300 to >1000 mg/dL). Thus, it is often used as a screening test while awaiting confirmation by quantitative protein excretion studies.

Patients with idiopathic nephrotic syndrome have a relatively inactive urine sediment (ie, oval fat bodies and hyaline casts, but few red cells and no red cell or other cellular casts). Hematuria is commonly seen in patients with glomerulonephritis, but does occur in focal segmental glomerulosclerosis (FSGS), and less commonly occurs with MCD. This was illustrated in the previously mentioned International Study of Kidney Disease in Children (ISKDC) study of 521 children who presented with primary nephrotic syndrome [3]. Hematuria was reported in 59 percent of patients with membranoproliferative glomerulonephritis, 49 percent of those with FSGS, and 23 percent of those with MCD.

Blood tests

Serum albumin — Hypoalbuminemia is one of the criteria that defines nephrotic syndrome. The serum albumin is typically below 3 g/dL (30 g/L) and can be as low as 1 g/dL (10 g/L). (See "Overview of heavy proteinuria and the nephrotic syndrome", section on 'Hypoalbuminemia'.)

Although serum albumin is reduced, total globulins are relatively preserved in patients with idiopathic nephrotic syndrome with either normal or slightly decreased serum alpha-1 globulin concentrations and increased alpha-2 and beta globulin. Gamma globulin concentrations vary depending upon the underlying disease. As examples, serum immunoglobulin G (IgG) is reduced in patients with MCD and is elevated in those with systemic lupus erythematous (SLE).

Lipids — Hyperlipidemia is a characteristic feature of nephrotic syndrome. Serum total cholesterol, triglycerides, and total lipids are elevated [16]. The increase in cholesterol is inversely correlated to the serum albumin concentration. (See "Lipid abnormalities in nephrotic syndrome".)

Renal function studies — Renal function is moderately impaired with elevation of serum creatinine in a minority of children with MCD primarily thought to be due to severe intravascular volume depletion [17].

Acute kidney injury (AKI) is a common occurrence in children who are hospitalized with NS [18]. Risk factors AKI in this group of patients include concurrent infection, exposure to nephrotoxic agents, and steroid-resistant NS [17,18].

Other studies

- Complete blood count − Hemoglobin and hematocrit may be increased in children with nephrotic syndrome, particularly MCD, as a result of plasma volume contraction. Thrombocytosis is common and platelet counts may reach 500,000 to 1 million counts/microL. Hemoconcentration and thrombocytosis may contribute to hypercoagulability and thrombotic complications. (See "Complications of nephrotic syndrome in children", section on 'Thromboembolism'.)
- Complement studies − Serum complement testing can be useful in the diagnosis of a specific renal or systemic disease that presents with nephrotic syndrome. Low C3 levels are typically seen in patients with membranoproliferative glomerulonephritis (MPGN) and postinfectious glomerulonephritis, while both low C3 and C4 are seen in patients with lupus nephritis. Serum complement is normal in patients with idiopathic nephrotic syndrome [3]. (See "Clinical presentation, classification, and causes of membranoproliferative glomerulonephritis" and "Poststreptococcal glomerulonephritis" and "Diagnosis and classification of renal disease in systemic lupus erythematosus".)
- Electrolytes − Hyponatremia can be present, due to decreased free water excretion resulting from hypovolemic stimulation of the release of antidiuretic hormone (ADH). Serum potassium may be high in oliguric patients. Serum calcium is low as a result of hypoproteinemia but ionized calcium is usually normal.

Initial therapy versus biopsy — Over 90 percent of patients with MCD will respond to steroid therapy within four weeks [5]. (See "Treatment of idiopathic nephrotic syndrome in children".)

As a result, steroid therapy can be initiated in patients who fulfill the following criteria for the clinical diagnosis of MCD without confirmation of the diagnosis by renal biopsy. This recommendation is based on both the high accuracy of clinical diagnosis and high response rate to steroid therapy.

- Age older than 1 year and less than 12 years (prepubertal)
- None of the following clinical findings are present: hypertension, gross hematuria, or a marked elevation in serum creatinine
- Normal complement levels

Using this approach, invasive renal biopsy can be avoided in 80 percent of children between 1 and 10 years of age who present with nephrotic syndrome [5]. Patients with steroid-responsive nephrotic syndrome typically have a favorable outcome. (See "Treatment of idiopathic nephrotic syndrome in children".)

DIFFERENTIAL DIAGNOSIS

Because children with nephrotic syndrome initially present with generalized edema, other causes of childhood generalized edema need to be considered in the differential diagnosis (table 1).

Nephrotic syndrome is distinguished from these causes of edema by the presence of nephrotic range proteinuria >50 mg/kg per day and hypoalbuminemia <3 g/dL (30 g/L) (see "Pathophysiology and etiology of edema in children"):

- Heart failure
- Other causes of hypoalbuminemia, such as protein-losing enteropathy or protein malnutrition (kwashiorkor). Hypoalbuminemia is also present in children with cirrhosis, but the main cause of fluid retention is portal hypertension. (See "Pathogenesis of ascites in patients with cirrhosis".)
- Increased capillary permeability due to an allergic reaction or hereditary angioedema. The edema in this setting is typically focal.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Nephrotic syndrome in children".)

SUMMARY AND RECOMMENDATIONS

- Nephrotic syndrome is diagnosed by fulfilling two defining characteristics: urine protein excretion (nephrotic range proteinuria) >50 mg/kg per day, and hypoalbuminemia defined as serum albumin <3 g/dL (30 g/L). (See 'Diagnosis' above.)
- Nephrotic syndrome is a result of injury to the glomerular filtration barrier, which increases its permeability. (See 'Pathogenesis' above.)
- The most common form of childhood nephrotic syndrome is primary idiopathic nephrotic syndrome. It is characterized by diffuse foot process effacement on electron microscopy and minimal changes (called minimal change disease [MCD]), primary focal segmental glomerulosclerosis (FSGS), or mesangial proliferation on light microscopy. MCD is particularly likely in children under the age of six. (See 'Idiopathic nephrotic syndrome' above and 'Epidemiology' above.)
- Idiopathic nephrotic syndrome generally presents with edema, usually first noted as periorbital edema. The edema can become generalized and massive (anasarca) resulting in peripheral edema, ascites, umbilical or inguinal hernias, scrotal or vulva swelling, and/or pleural effusions. (See 'Clinical manifestations' above.)
- Macroscopic hematuria and elevated blood pressure may be present. The presence of either one of these findings makes it less likely that MCD is present, and another renal disease should be considered. (See 'Clinical manifestations' above.)
- Initial laboratory testing confirms the diagnosis of nephrotic syndrome and may also be used to diagnose specific underlying causes of nephrotic syndrome. (See 'Diagnostic evaluation' above.)
- In children with nephrotic syndrome who have a high probability of having MCD based upon clinical and laboratory findings, we recommend empiric therapy with oral prednisone, thus avoiding renal biopsy (**Grade 1B**). Renal biopsy is performed in patients who fail to respond to steroid therapy (steroid-resistant nephrotic syndrome) and in those who are less likely to initially respond to steroid therapy. (See "Treatment of idiopathic nephrotic syndrome in children", section on 'Steroid-resistant nephrotic syndrome' and 'Minimal change disease' above.)
- The differential diagnosis includes other diseases that present with edema; these disorders are easily differentiated from nephrotic syndrome by the presence of nephrotic range proteinuria and hypoalbuminemia (See 'Differential diagnosis' above.)

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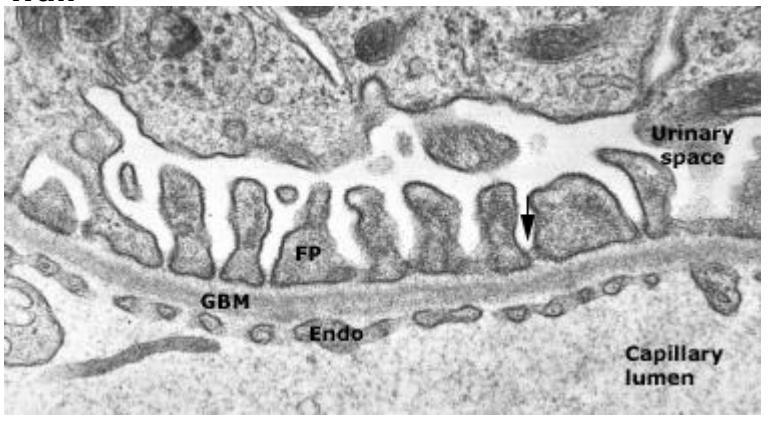
GRAPHICS

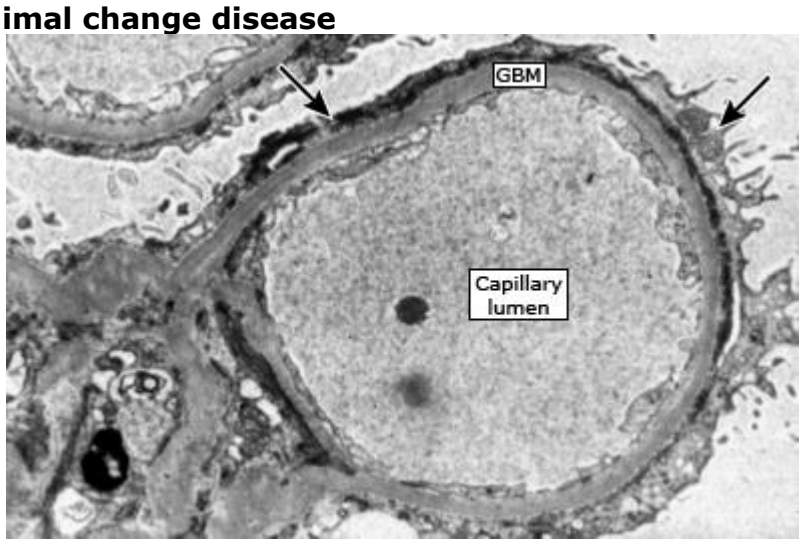
Normal glomerular capillary wall



High power electron micrograph shows the three layers of the normal glomerular capillary wall: the fenestrated endothelium (Endo); the glomerular basement membrane (GBM); and the epithelial cell with its foot processes (FP). The foot processes are separate by slit pores which are closed by a thin membrane, the slit diaphragm (arrow). In terms of permeability to macromolecules, the GBM and the slit diaphragms are the major sites of size-selectivity, while the endothelium and GBM are the major sites of charge-selectivity.

Courtesy of Helmut Rennke, MD.
Graphic 72505 Version 1.0

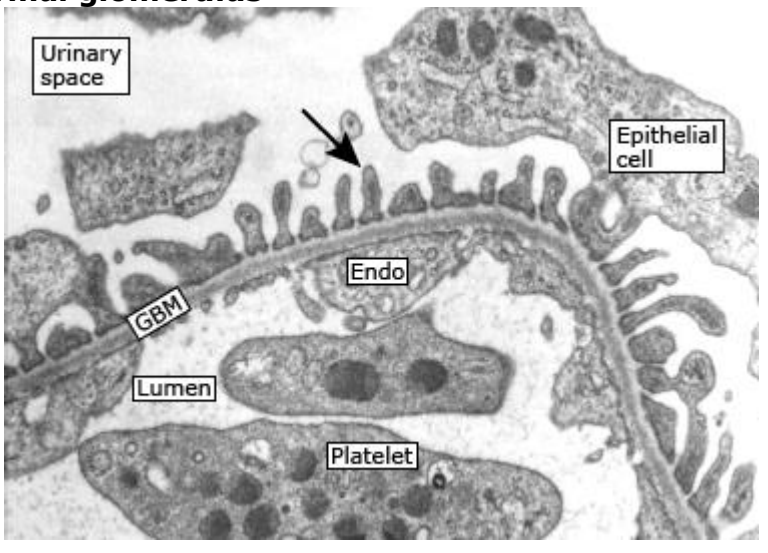
Electron microscopy in minimal change disease



Electron micrograph in minimal change disease showing a normal glomerular basement membrane (GBM), no immune deposits, and the characteristic widespread fusion of the epithelial cell foot processes (arrows).

Courtesy of Helmut Rennke, MD.
Graphic 58414 Version 4.0

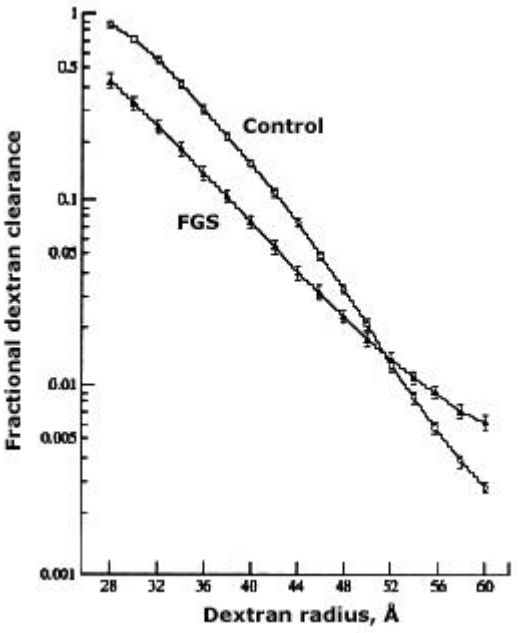
Electron micrograph of a normal glomerulus



Electron micrograph of a normal glomerular capillary loop showing the fenestrated endothelial cell (Endo), the glomerular basement membrane (GBM), and the epithelial cells with its interdigitating foot processes (arrow). The GBM is thin, and no electron-dense deposits are present. Two normal platelets are seen in the capillary lumen.

Courtesy of Helmut G Rennke, MD.
Graphic 50018 Version 7.0

Mechanism of proteinuria in FGS



Dextran sieving profiles in patients with heavy proteinuria and the nephrotic syndrome due to focal glomerulosclerosis (FGS). A fractional dextran clearance of 1 represents complete filtration. Patients with FGS have decreased clearance of smaller dextrans, but increased clearance of dextrans with a radius above 52 Å, suggesting an increased number of larger pores.

Data from Guasch A, Hashimoto H, Sibley RK, et al. Am J Physiol 1991; 260:F728.
Graphic 76597 Version 2.0

Causes of edema in childhood

Generalized edema
Increased capillary hydrostatic pressure
Increased plasma volume from sodium and water retention
Heart failure
(Localization can be seen in some cardiac disease)
Primary renal disease
Acute glomerulonephritis
Renal failure (acute/chronic)
Nephrotic syndrome
Drug induced
Vasodilators (eg, minoxidil)
Dihydropyridine calcium channel blockers (eg, nifedepine and amlodipine)
Venous obstruction
Hepatic cirrhosis
Decreased capillary oncotic pressure (Hypoalbuminemia)
Nephrotic syndrome
Liver failure
Protein losing enteropathy
Protein malnutrition (kwashiorkor)
Increased capillary permeability
Burn

Sepsis
Localized edema
Increased capillary hydrostatic pressure
Venous obstruction
Extrinsic compression (tumor or lymphadenopathy)
Venous thrombosis
Increased interstitial hydrostatic pressure
Lymphatic obstruction
Primary
Turner syndrome
Noonan syndrome
Milroy's disease
Lymphedema praecox
Secondary
Lymphadenitis
Granulomatous lymphangitis
Autoimmune disease (juvenile idiopathic arthritis & Crohn's disease)
Increased capillary permeability
Angioedema
Allergic reaction
Hereditary angioedema

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Contributor Disclosures

Patrick Niaudet, MD Nothing to disclose**Tej K Mattoo, MD, DCH, FRCP**Consultant/Advisory Boards: Kite Medical Limited [Vesicoureteral reflux (Bioimpedance)].**Melanie S Kim, MD**Nothing to disclose

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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