

The Nephrotic Syndrome

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The nephrotic syndrome is a constellation of renal and extrarenal manifestations that can be caused by a multitude of systemic diseases as well as by primary insults to the kidney. The prevalence of the syndrome depends largely on the underlying causes, which vary significantly by age of onset. The nephrotic syndrome is classically characterized by 6 main abnormalities of which proteinuria of greater than 3.5 g/24 hr is the cornerstone. The cardinal manifestations of the nephrotic syndrome include edema, hypoalbuminemia, hyperlipidemia, and lipiduria. Hypercoagulability is also a well-known complication of the nephrotic syndrome. Because of the diversity of disease processes that can cause the nephrotic syndrome, the prognosis and treatment vary dramatically depending on the underlying etiology. This article reviews the presentation, complications, and common underlying causes of the nephrotic syndrome and briefly discusses the diagnostic work-up and treatment.

CLINICAL PRESENTATION AND COMPLICATIONS

The presentation of the nephrotic syndrome includes edema, hypoalbuminemia, and hyperlipidemia. Some patients may present with complications of the nephrotic syndrome as their initial manifestation, and these include cardiovascular events, thromboembolism, infections, malnutrition, anemia, and hypocalcemia (Table 1).

Edema

Edema is the most profound symptom of the nephrotic syndrome. It may present in a mild localized form or in a generalized fashion and also may be mobile, presenting as puffiness of the eyelids that is worsened with lying down, especially in the morning upon awakening, and as lower extremity edema that is worse at the end of the day. Moreover, excess fluid may collect internally and present as pleural or pericardial effusions and ascites. Subungual edema may manifest as parallel white lines in the fingernail beds. In cases of severe edema, the patient may have generalized swelling, or anasarca, which is usually pitting and worse in dependent areas of

CHARACTERISTIC FEATURES OF THE NEPHROTIC SYNDROME

- Proteinuria exceeding 3.5 g/24 hr
- Hyperlipidemia
- Lipiduria
- Edema
- Hypoalbuminemia
- Hypercoagulability

the body such as the genitalia and lower extremities. Because of the excess body fluid, patients generally report unexplained weight gain and fatigue.

Edema of the nephrotic syndrome may be a manifestation of hypoalbuminemia with increased water and salt retention, or it may be due to a primary defect within the collecting tubule of the nephron that leads to uncontrolled water and salt retention. Regardless of the pathophysiology of edema, it is important to consider other conditions that present with edema and/or hypoalbuminemia (Table 2).

Hypoalbuminemia

In nephrotic syndrome, the serum concentration of albumin often is significantly low as it is one of the smaller proteins and therefore is easily lost in the urine. When albumin appears in the urine, the patient may complain of urine frothiness. Albumin synthesis is upregulated by the liver because of the urinary losses, but the body's compensatory mechanisms to maintain albumin homeostasis are insufficient as urinary losses exceed hepatic production.

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Table 1. Complications of the Nephrotic Syndrome

Increased cardiovascular risk
Thrombosis and thromboembolism
Increased risk of infections
Protein malnutrition
Iron-resistant microcytic hypochromic anemia
Vitamin D deficiency and hypocalcemia

Hyperlipidemia

The other characteristic findings in the nephrotic syndrome may present clinically as medical complications. The hyperlipidemia associated with the syndrome is primarily due to abnormal lipoprotein homeostasis that results in an increase in synthesis and decrease in catabolism. Patients usually have elevations of total plasma cholesterol, triglyceride, very-low-density lipoprotein (VLDL), and low-density lipoprotein (LDL).¹ Dyslipidemia increases the risk of atherosclerosis and cardiovascular disease in patients with the nephrotic syndrome, and patients may present with complications of these diseases.

Hypercoagulability

The hypercoagulable state associated with the nephrotic syndrome is caused by an increased urinary loss of antithrombin III, altered activity and levels of proteins C and S, increased hepatic synthesis of fibrinogen, and increased platelet aggregation. Clearly, these conditions predispose patients to an increased risk of spontaneous thrombosis and embolism. In adults, most thromboses are venous, while in children arterial thromboses are more common.² Renal vein thrombosis is present in approximately 30% of patients with the nephrotic syndrome, and the rate is highest in patients with membranous glomerulopathy.^{3,4} The patient with acute renal vein thrombosis can present with sudden onset of flank or abdominal pain, gross hematuria, and an acute decline in renal function, but most patients are asymptomatic.⁴ In addition to renal vein thrombosis, 20% to 30% of nephrotic patients develop pulmonary emboli.³ Strokes and myocardial infarctions are also potential complications that can occur as a result of the hypercoagulable state associated with the nephrotic syndrome.^{5,6}

Immunocompromised State

The nephrotic syndrome is associated with increased urinary loss of immunoglobulins, especially IgG, as well as defects in the complement cascade.

Table 2. Other Causes of Edema and Hypoalbuminemia

Congestive heart failure
Constrictive pericarditis
Liver disease
Protein-losing enteropathy
Malnutrition
Myxedema
Lymphedema

Each of these defects weakens the immune system and increases susceptibility to infections. The pneumococcal vaccine, commonly given to patients with nephritic syndrome, may have limited efficacy due to a rapid decline of antipneumococcal antibody levels.⁷

Anemia

Patients with nephrotic-range proteinuria have a tendency to lose different types of proteins in the urine, including binding proteins. With transferrin loss due to proteinuria, patients present with an iron-resistant microcytic hypochromic anemia. With progressive renal failure, anemia may result from decreased renal synthesis of erythropoietin.⁸

PRIMARY CAUSES

There are 6 main causes of nephrotic syndrome. Of the primary renal causes, minimal change disease, focal segmental glomerulosclerosis (FSGS), membranous glomerulopathy, and membranoproliferative glomerulonephritis (MPGN) are the most common, while diabetic nephropathy and systemic amyloidosis constitute the most common secondary causes (**Table 3**). The commonly used term *primary nephrotic syndrome* is somewhat of a misnomer in that there may in fact be an associated underlying disease or trigger for the syndrome. The classification of primary nephrotic syndromes is primarily based on histopathology. The term *secondary nephrotic syndrome* relates to a more clearly defined underlying disease process such as diabetes.

Minimal Change Disease

Minimal change disease is the most common cause of nephrotic syndrome in children, accounting for 80% of all cases in children aged 4 to 8 years. It is also responsible for 20% of all cases in adults.⁹ The hallmark of minimal change disease is the presence of normal-appearing glomeruli on light microscopy of a renal biopsy specimen (**Figure 1**) but effacement of the foot processes of the epithelial cells on electron microscopy

Table 3. Most Common Primary Causes of the Nephrotic Syndrome

	Causes	Microscopic Characteristics
Minimal change disease	Mostly idiopathic	Effacement of foot processes on electron microscopy
Focal segmental glomerulosclerosis	Primary: idiopathic, genetic Secondary: sickle cell disease, reflux nephropathy, heroine use, HIV, cyclosporine toxicity	Sclerosis and hyalinosis of segments of less than 50% of all glomeruli with electron microscopy
Membranous glomerulopathy	Hepatitis B, SLE, malignancies, penicillamine, gold	Thickening of the glomerular basement membrane with electron microscopy; IgG and C3 deposits with immunofluorescent staining
Membranoproliferative glomerulonephritis	HIV, hepatitis B, hepatitis C, cryoglobulinemia, SLE, malignancies	Type I: subendothelial and mesangial immune deposits with electron microscopy; decreased plasma levels of C1q, C4, C3 Type II: intramembranous dense deposits with electron microscopy; decreased plasma levels of C3

SLE = systemic lupus erythematosus.

(Figure 2).¹⁰ This disease has a tendency to manifest following an upper respiratory infection or immunizations, but the majority of cases are idiopathic. Minimal change disease tends to represent the benign extreme on a spectrum of severity in the nephrotic syndrome.

Focal Segmental Glomerulosclerosis

FSGS accounts for one third of the cases of the nephrotic syndrome in adults and almost 50% of cases among African Americans.^{11,12} Patients usually present with nephrotic-range proteinuria, hypertension, renal insufficiency, and possibly hematuria. There are several primary and secondary causes of renal insults leading to FSGS. Secondary FSGS may present in association with HIV infection, heroin use, sickle cell disease, obesity, and reflux nephropathy.^{13,14} Most cases of primary FSGS are idiopathic, although 15% to 20% are familial.¹⁴ FSGS is classically described as the sclerotic involvement of only parts of less than 50% of the glomeruli on renal biopsy (Figure 3). The sclerotic segments usually contain IgM and C3 deposits. FSGS has a worse response to treatment and poorer prognosis compared with minimal change disease and membranous glomerulopathy. Factors associated with a poor prognosis include African American ethnicity, abnormal renal function, and steroid-resistant heavy proteinuria.¹³

Membranous Glomerulopathy

Membranous glomerulopathy is one of the most common primary renal causes of the nephrotic syndrome, accounting for 30% to 40% of all cases in adults.⁹ There is a male predominance, and the incidence usually peaks between ages 30 and 50 years. Approximately 75% of patients present with nephrotic-range proteinuria, and 50% present with microscopic

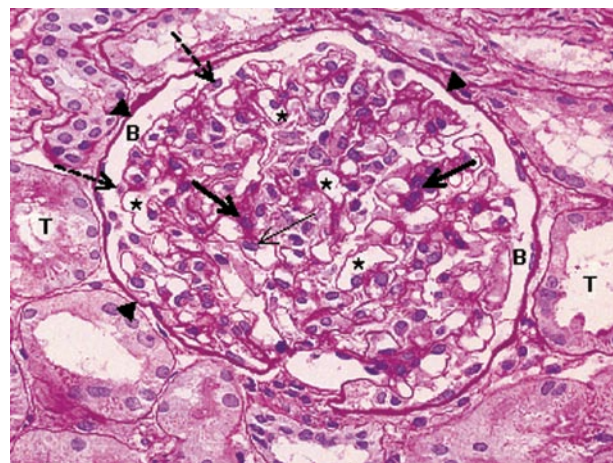


Figure 1. Normal glomerulus on light microscopy. Thick arrows = mesangial cells; thin arrow = glomerular endothelial cell; * = capillary lumen; B = Bowman's space; dashed arrows = podocytes; arrowheads = Bowman's capsule; T = tubule. (Reprinted with permission from Pichlet RH, Shankland SJ. Glomerular disease. In: Dale DC, Federman DD, editors. ACP Medicine: nephrology. New York: WebMD; 2006.)

hematuria.¹⁵ On renal biopsy, membranous glomerulopathy is characterized by the presence of diffuse thickening of the glomerular basement membrane, granular deposition of IgG and C3, and the absence of inflammatory mediators (Figure 4). Between 20% and 30% of nephrotic patients with biopsy-proven membranous glomerulopathy have an underlying systemic disease (eg, systemic lupus erythematosus [SLE], hepatitis B, or malignancy) or drug-induced disease, classically from chronic gold or penicillamine drug therapy.¹⁵ Nonsteroidal anti-inflammatory drugs (NSAIDs) are also implicated in membranous nephropathy; NSAID-induced disease is considered an idiosyncratic reaction that resolves upon discontinuation of the drug.¹⁶

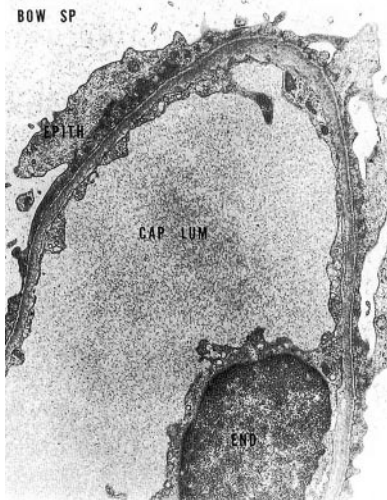


Figure 2. Electron micrograph of a glomerular capillary showing effaced foot process of epithelial cell (EPITH) in minimal change disease. END = endothelial cell; BOW SP = Bowman's space; CAP LUM = capillary lumen. (Reprinted with permission from Greenberg A, editor. *Primer on kidney diseases*. 4th ed. Philadelphia: Saunders; 2005:166. Copyright 2005 National Kidney Foundation.)

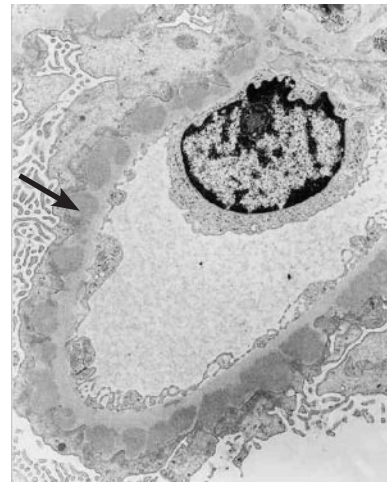


Figure 4. Electron microscopy showing characteristic sub-epithelial immune deposits in membranous nephropathy (arrow). (Reprinted with permission from J. Charles Jennette, MD, and F.W. Maddux, MD.)

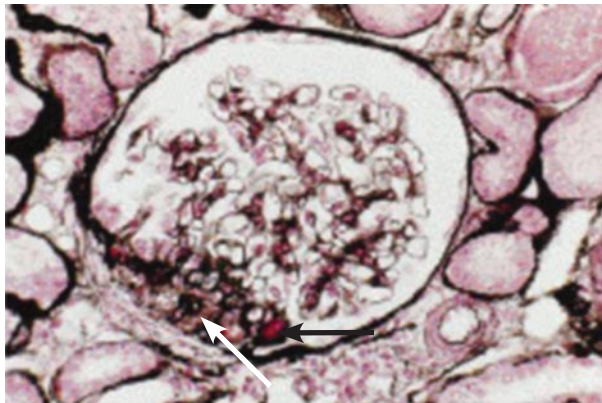


Figure 3. Segmental obliteration of capillary lumina (white arrow) and a large hyalin deposit (black arrow) in focal segmental glomerulosclerosis. (Reprinted with permission from Orth SR, Ritz E. *The nephrotic syndrome*. *N Engl J Med* 1998;338:1205. Copyright © 1998 Massachusetts Medical Society. All rights reserved.)

Membranoproliferative Glomerulonephritis

MPGN accounts for 5% to 10% of all cases of the nephrotic syndrome⁹ and is more common in children and young adults. It may manifest as a mixed clinical picture with nephritic and nephrotic components and can also present as asymptomatic proteinuria and hematuria detected on routine urinalysis. MPGN type I is an immune complex glomerulonephritis associated with chronic infections (eg, HIV and hepatitis B

and C), systemic immune complex diseases (eg, SLE, cryoglobulinemia), and malignancies.¹⁷ Patients with MPGN type I usually present with heavy proteinuria and are found to have decreased levels of C3, C1q, and C4. On renal biopsy, type I is characterized by subendothelial and mesangial immune deposits. MPGN type II tends to be autoimmune, and patients usually present with nephrotic-range proteinuria and sometimes with recurrent macroscopic hematuria, which is more characteristic of the nephritic syndrome. Type II is also associated with dense deposits in the glomerular basement membrane (Figure 5). Patients are found to have decreased plasma levels of C3, normal levels of C1q and C4, and a circulating antibody called the C3 nephritic factor.¹⁷

SECONDARY CAUSES

Diabetes

Diabetic nephropathy is the most common secondary cause of the nephrotic syndrome in adults.¹⁸ Moreover, it is the leading cause of end-stage renal disease in Western societies and is responsible for more than 30% of cases of end-stage renal disease requiring dialysis.¹⁹ Diabetic nephropathy complicates 30% of cases of type 1 diabetes mellitus and up to 50% of cases of type 2 diabetes mellitus.²⁰

Diabetic nephropathy is characterized by a progressive rise in urine albumin excretion combined with an elevated blood pressure and a decline in glomerular filtration rate.^{19,21,22} The diagnosis of diabetic nephropathy is defined by the presence of proteinuria

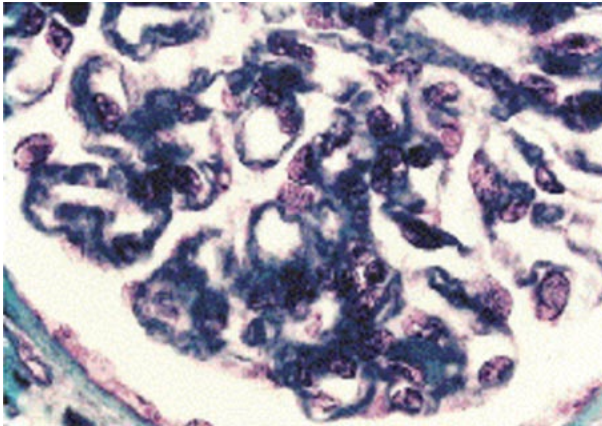


Figure 5. Marked widespread thickening of the basement membrane due to dense deposits in membranoproliferative glomerulonephritis type II (dense deposit disease). (Reprinted with permission from Orth SR, Ritz E. The nephrotic syndrome. *N Engl J Med* 1998;338:1205. Copyright © 1998 Massachusetts Medical Society. All rights reserved.)

exceeding 500 mg/24 hr.²³ However, most patients initially present with microalbuminuria on routine urinalysis and are generally asymptomatic. This initial rise in urinary protein excretion in patients with diabetes is small, hence use of the term *microalbuminuria*, which is defined as 30 to 300 mg of albumin in a 24-hour urine collection. Because a 24-hour urine collection is not always practical, the first step in screening for diabetic nephropathy is measurement of a spot urine sample for albumin.²³ The albumin measurement can be expressed as urinary albumin-to-creatinine ratio (mg/g); the normal ratio is less than 30.²⁴ Although a renal biopsy is not necessary for a diagnosis of diabetic nephropathy, some of the characteristic findings on biopsy include thickening of the glomerular basement membrane, mesangial expansion, and nodular expansion of the extracellular matrix (ie, Kimmelstiel-Wilson nodular glomerulosclerosis; **Figure 6**).²³ Risk factors for the development of diabetic nephropathy include uncontrolled hyperglycemia, systemic hypertension, glomerular hypertension, proteinuria, cigarette smoking, dyslipidemia, and genetic predisposition.

Systemic Amyloidosis

Systemic amyloidosis is a disease that more commonly affects older adults with systemic involvement. It may be primary, resulting from a monoclonal plasma cell dyscrasia, or secondary, resulting from an underlying chronic inflammatory disease such as long-standing rheumatoid arthritis or inflammatory bowel disease.^{25,26} It is associated with the proliferation and deposition of insoluble monoclonal immunoglobulin light chains in the extracellular

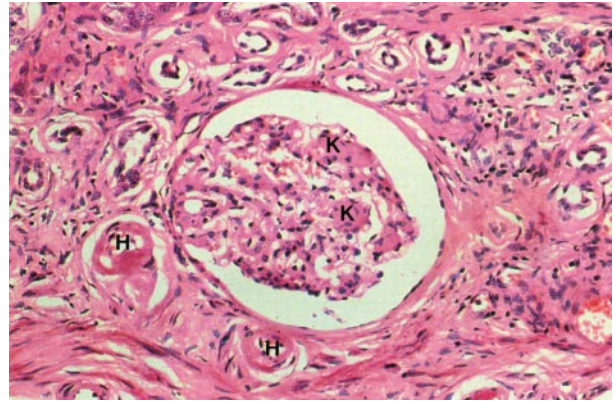


Figure 6. Nodular diabetic glomerulosclerosis. H = arteriolar hyalinization; K = Kimmelstiel-Wilson nodules. (Adapted from Wheeler PR, Burkitt HG, Stevens A, Lowe JS. Basic histopathology: a colour atlas and text. New York: Churchill Livingstone; 1985:134. Copyright © 1985, with permission from Elsevier.)

matrix of smooth and striated muscles, connective tissues, blood vessel walls, and peripheral nerves. Given this pathophysiology, patients may present with unexplained nephrotic syndrome, cardiac dysfunction, neuropathy, and organomegaly. Kidney dysfunction is the most common presenting problem.²⁷ The diagnostic hallmark is the presence of apple-green birefringence when specimens of amyloid deposits are stained with Congo red and viewed under polarized light.

DIAGNOSTIC EVALUATION

After a careful investigation of the patient's history and physical examination, the initial and most valuable diagnostic laboratory test in the work-up for suspected nephrotic syndrome is the evaluation of a urine specimen to assess and quantify the amount of protein present. Once the presence of nephrotic-range proteinuria is confirmed, further diagnostic evaluation is necessary to investigate the other characteristics of the nephrotic syndrome. Serum albumin levels, a lipid panel, plasma creatinine level, and glomerular filtration rate calculation should be obtained. Further diagnostic evaluation is directed by the history and physical examination. If new-onset diabetes with diabetic nephropathy is suspected, measurement of fasting plasma glucose is warranted. If multiple myeloma is a possibility, serum calcium and serum and urine protein electrophoresis should be obtained. Antinuclear antibody as well as other circulating autoantibodies may be measured if there is a suspicion of an immune complex disease or a collagen vascular disease. Hepatic enzymes (aspartate aminotransferase and alanine aminotransferase) as well as serologic tests for hepatitis B and C and HIV infection may be necessary.

Careful examination of the urine sediment also may help direct the diagnosis. With the nephrotic syndrome, granular, fatty, hyaline, or waxy epithelial cell casts may be present. Sudan staining may help identify oval fat bodies, which can be found in some cases because of the lipiduria associated with the nephrotic syndrome.

The need for imaging studies is rather limited. A chest radiograph may be warranted if pleural effusion is suspected. Otherwise, renal ultrasonography is the main imaging study necessary to exclude any congenital or developmental abnormalities of the kidney. It will also assess the size and echogenicity of the kidneys, which may direct the diagnosis.

Renal biopsy to determine the diagnosis is crucial. A prospective study showed that the results of renal biopsy altered the management in 86% of patients with nephrotic-range proteinuria.²⁸ Because of the diversity of causes leading to the common characteristics of the nephrotic syndrome, the evaluation of renal histology is pertinent in establishing the diagnosis. Referral to a nephrologist should be pursued at that time to ensure accurate treatment and management.

TREATMENT

Since proteinuria is the main manifestation of nephrotic syndrome and the cause of its complications, several measures should be implemented to help reduce the proteinuria. The use of angiotensin-converting enzyme inhibitors is the most important intervention, even in normotensive patients. In addition, a low-protein diet has been shown to help reduce the proteinuria, with a recommended daily protein intake of 0.7 g/kg/day. Patients should be carefully monitored, however, to avoid malnutrition.⁹

The treatment of the nephrotic syndrome varies based on the severity of the complications. Edema is usually controlled by adherence to a low-salt diet and the use of diuretics. Because nephrotic patients have abnormally increased tubular reabsorption of sodium, patients are advised to limit their sodium chloride intake to 2 g/day. For mild cases of edema, salt restriction is coupled with a mild diuretic such as a thiazide. For moderate to severe cases of edema, a loop diuretic is usually added.

The hyperlipidemia associated with the nephrotic syndrome may be managed with nonpharmacologic interventions such as the use of soy protein diet to lower the total cholesterol and LDL levels. The use of fish oil has been shown to lower triglycerides and VLDL.²⁹ Statins are the mainstay of treatment as they have been proven to reduce LDL levels.

Because nephrotic patients are also susceptible to infections, the pneumococcal vaccine is usually

recommended, although the benefit is not well studied.^{7,30} In addition, many studies have shown that prophylactic anticoagulation therapy helps reduce the incidence of pulmonary embolism and renal vein thrombosis in patients with the nephrotic syndrome, especially patients with membranous glomerulopathy.³

Most of the causes of the nephrotic syndrome respond to immune therapy treatment. Minimal change disease in adulthood is usually treated with prednisolone, and cyclophosphamide may be added in cases of relapse or steroid resistance. FSGS has a poor response to steroid treatment, and most patients have an improved response to combined cyclosporine therapy with prednisolone.³¹ After excluding secondary causes of membranous glomerulopathy, patients are treated with alternating monthly cycles of methylprednisolone and chlorambucil.^{32,33} In cases of rapidly progressive renal loss and renal failure, dialysis and kidney transplantation become considerations.

CONCLUSION

The nephrotic syndrome is a common constellation of abnormalities that includes proteinuria, edema, hyperlipidemia, lipiduria, hypoalbuminemia, and hypercoagulability. It can be caused by underlying systemic diseases or direct injury to the kidney. Several causes of the nephrotic syndrome have characteristic findings on renal biopsy. A careful evaluation of nephrotic patients is essential for optimal care and management. **HP**

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