

Minimal Change Glomerulopathy

Epidemiology

Minimal change glomerulopathy, also known as minimal change disease, was first described in 1913 by Monk who called it "lipoid nephrosis" because of the lipid in the tubular epithelial cells and urine.^[111] Minimal change glomerulopathy is most common in children, accounting for 70% to 90% of nephrotic syndrome in children younger than

Figure 28-1 Graph depicting the frequencies of different forms of glomerular disease identified in renal biopsy specimens from patients with proteinuria of greater than 3 g/day evaluated in the University of North Carolina Nephropathology Laboratory. Some diseases that cause proteinuria are underrepresented because they are not always evaluated by renal biopsy. For example, many patients with steroid-responsive proteinuria may be given a presumptive diagnosis of minimal change glomerulopathy and not subjected to biopsy, and most patients with diabetes and proteinuria are presumed to have diabetic glomerulosclerosis and are not biopsied.

age 10 years and 50% in older children. Minimal change glomerulopathy also causes 10% to 15% of primary nephrotic syndrome in adults ([Fig. 28-1](#)).

The incidence of minimal change glomerulopathy has geographic variations. Minimal change glomerulopathy is more common in Asia than in North America or Europe.^[112] This may be a consequence of differences in renal biopsy practices, or of differences in environmental or genetic influences. The disease may also affect elderly patients in whom there is a higher propensity for the clinical syndrome of minimal change glomerulopathy and acute renal failure (discussed later). There appears to be a male prevalence of this process in some series, especially in children in whom the male-to-female ratio is 2 to 3:1.^[113] Our own data, however, do not support this ([Table 28-7](#)).

Pathology

LIGHT MICROSCOPY

Minimal change glomerulopathy has no glomerular lesions by light microscopy ([Fig. 28-2](#)), or only minimal focal segmental mesangial prominence. This mesangial prominence should have no more than three cells embedded in the matrix of a segment, and the matrix should not be expanded to the extent that capillary lumens are compromised. Capillary walls should be thin and capillary lumens patent.

The most consistent tubular lesion is increased protein and lipid resorption droplets in tubular epithelial cells. These droplets are periodic acid-Schiff positive. Conspicuous resorbed lipid in epithelial cells prompted the designation lipoid nephrosis for this disease before the recognition of the ultrastructural glomerular lesion. Interstitial edema is rare,

TABLE 28-7 -- Sex and Race Predilections of Diseases That Cause the Nephrotic Syndrome

GLOMERULAR LESION	<i>N</i>	MALE-FEMALE RATIO	WHITE-BLACK RATIO
Minimal change glomerulopathy	522	1.1:1.0	1.9:1.0
FSGS (typical)	1103	1.4:1.0	1.0:1.0
Collapsing glomerulopathy variant of FSGS	135	1.2:1.0	1.0:7.8
Glomerular tip lesion FSGS	94	1.0:1.0	4.7:1.0
Membranous glomerulopathy	1120	1.4:1.0	1.9:1.0
C1q nephropathy	114	1.0:1.0	1.0:4.8
Fibrillary glomerulonephritis	76	1.0:1.2	14.3:1.0
FSGS, focal segmental glomerulosclerosis.			

*Information in this table is from 9605 native kidney biopsies from the University of North Carolina Nephropathology Laboratory. This laboratory evaluates kidney biopsies from a base population of approximately 10 million throughout the southeastern United States and centered in North Carolina. The expected white-to-black ratio in this renal biopsy population is approximately 2:1.

Figure 28-2 Unremarkable light microscopic appearance of minimal change glomerulopathy. Glomerular basement membranes are thin, and there is no glomerular hypercellularity or mesangial matrix expansion. (Jones methenamine silver, $\times 300$.)

even in patients with severe nephrotic syndrome and anasarca. Focal proximal tubular epithelial flattening (simplification), which is histologically identical to that seen with ischemic acute renal failure, occurs in patients who have the syndrome of minimal change glomerulopathy with acute renal failure.^[114]

Focal areas of interstitial fibrosis and tubular atrophy in a specimen that otherwise looks like minimal change glomerulopathy, especially in a young person, should raise the possibility of focal segmental glomerulosclerosis that was not sampled in the biopsy specimen. Examination of additional levels of section may reveal a sclerotic glomerulus.

IMMUNOFLUORESCENCE MICROSCOPY

Glomeruli usually show no staining with antisera specific for IgG, IgA, IgM, C3, C4, or C1q. The most frequent positive finding is low-level mesangial staining for IgM, sometimes accompanied by low-level staining for C3. If this IgM staining is not accompanied by mesangial dense deposits identified by electron microscopy, it is consistent with a diagnosis of minimal change glomerulopathy. Patients with mesangial IgM by immunofluorescence microscopy (in the absence of electron dense deposits) do not have a worse prognosis than those without IgM.^{[115] [116]} The presence of mesangial electron dense deposits worsens the prognosis and thus justifies altering the diagnosis, for example, to IgM mesangial nephropathy.^[117] Anything more than trace staining for IgG or IgA casts substantial doubt on a diagnosis of minimal change glomerulopathy. Even when no sclerotic glomerular lesions are seen by light microscopy, well-defined irregular focal segmental staining for C3 and IgM should raise the possibility of focal segmental glomerulosclerosis because sclerotic lesions usually trap C3 and IgM. Glomerular and tubular epithelial cell cytoplasmic droplets, and tubular casts, may stain positively for immunoglobulins and other plasma proteins when there is substantial proteinuria.

ELECTRON MICROSCOPY

The pathologic sine qua non of minimal change glomerulopathy is effacement of visceral epithelial cell foot processes observed by electron microscopy ([Fig. 28-3](#) and [Fig. 28-4](#)). However, this is not a specific feature, because it occurs in the glomeruli of patients with severe proteinuria of any cause. During active nephrosis, the effacement often is very extensive, with only a few scattered intact foot processes. As the patient enters remission, the extent of foot process effacement diminishes. The effacement usually is accompanied by microvillous transformation, which is the development of numerous villous projections from the epithelial surface into the urinary space. The effacement also is accompanied by increased density of the cytoskeleton, including actin filaments, in clumps near the basement membrane surface of the visceral epithelial cells. These intracytoplasmic densities should not be confused with subepithelial immune complex dense deposits. Glomerular and proximal tubular epithelial cells have increased clear and dense cytoplasmic droplets.

All of these ultrastructural glomerular changes occur in other glomerular diseases when there is nephrotic-range proteinuria. Therefore, minimal change glomerulopathy is a

Figure 28-3 Diagrams depicting the ultrastructural features of a normal glomerular capillary loop (**A**) and a capillary loop with features of minimal change glomerulopathy (**B**). The latter has effacement of epithelial foot processes (*arrow*) and microvillous projections of epithelial cytoplasm. (*Used with permission from J.C. Jennette.*)

Figure 28-4 Electron micrograph of a glomerular capillary wall from a patient with minimal change glomerulopathy showing extensive foot process effacement (*arrows*) and microvillous transformation (magnification $\times 5000$).

diagnosis by exclusion that is made only when there is no evidence by light, immunofluorescence, or electron microscopy of any other glomerular disease.

Pathogenesis

Although the pathogenesis of minimal change glomerulopathy remains unclear, this disorder is most likely a consequence of T lymphocyte abnormalities.^[118] Several observations support this contention.^{[118] [119] [120] [121] [122]} Specifically, corticosteroids and alkylating drugs cause a remission of minimal change glomerulopathy, there is an association of minimal change glomerulopathy with Hodgkin disease,^{[123] [124]} and remissions are associated with depression of cell-mediated immunity during viral infections such as measles. Specific evidence stems from the finding that a glomerular permeability factor is produced by human T cell hybridomas obtained from a patient with minimal change nephrosis. When this factor was injected into rodents, proteinuria occurred with partial fusion of glomerular epithelial cell foot processes.^[125] While there are no observable abnormalities in T or B cell populations in patients with relapsing or quiescent minimal change glomerulopathy,^{[126] [127] [128] [129]}

lymphocytes have depressed reactivity when challenged with mitogens.^{[68] [130] [131] [132] [133] [134] [135] [136] [137]} T cells apparently produce a product, most likely a lymphokine, which increases glomerular permeability to protein. When the glomerular permeability factor is removed from the kidney, it functions normally. This is supported by the intriguing observation that transplantation of a kidney from a patient with refractory minimal change glomerulopathy resulted in rapid disappearance of proteinuria.^[138]

This factor may have specificity for glomerular epithelial cells that results in loss of the charge-selective barrier of the GBM. The loss of charge selectivity has been assessed by dextran studies.^{[139] [140]} In these studies, there is less evidence of a defect in the size-

selective barrier and more of an alteration of the basement membrane electrostatic charge. The glomerular negative charge is reduced in relapse. ^[141]

There are other potential pathogenic mechanisms for the pathologic changes described as minimal change glomerulopathy. Circulating immune complexes have been found in patients who have been presumed to have minimal change glomerulopathy, ^[142] ^[143] the level of which fell during remission. Moreover, there have been studies of the presence of an IgM rheumatoid factor in patients with minimal change glomerulopathy. The significance of these observations is questionable given the lack of immune complex deposition within glomeruli.

Clinical Features and Natural History

The cardinal clinical feature of minimal change glomerulopathy in children is the relatively abrupt onset of proteinuria and development of the nephrotic syndrome with heavy proteinuria, hypoalbuminemia, and hyperlipidemia. The edematous picture is typically what prompts the parents of children to seek medical attention. Hematuria is distinctly unusual, and in children, hypertension is not common. In the International Study of Kidney Diseases in Children (ISKDC) series, ^[144] diastolic hypertension was found in 13% of patients. ^[145] The clinical features of adults with minimal change glomerulopathy tend to be somewhat different. In a group of 89 adults over the age of 60, hypertension, sometimes severe, as well as renal insufficiency, was more common. ^[146] Because individuals over the age of 60 account for almost one fourth of adult patients with minimal change glomerulopathy, this presentation must be considered.

Minimal change glomerulopathy has been associated with several other conditions, including viral infections, pharmaceutical agents, malignancy, and allergy ([Table 28-8](#)). In some patients, there is a history of drug reaction before the onset of minimal change glomerulopathy. The use of nonsteroidal anti-inflammatory drugs and, particularly, fenoprofen has been associated with, and may cause, minimal change glomerulopathy. ^[147] In this setting, most patients have not only proteinuria but also pyuria and renal insufficiency as a consequence of the simultaneous development of an acute tubulointerstitial nephritis. This same process has also been described with other compounds, including interferon, ^[148] penicillins, and rifampin. In most patients, discontinuation of the offending drug leads to resolution of the proteinuria, but it may take weeks to months for complete amelioration of pyuria and renal insufficiency.

Rarely, minimal change glomerulopathy is associated with a lymphoid malignancy, usually Hodgkin disease. ^[149] Minimal

TABLE 28-8 -- Common Disease Associations with Minimal Change Glomerulopathy
Infections
Viral
Parasitic
Pharmaceutical agents
Nonsteroidal anti-inflammatory drugs
Gold
Lithium
Interferon
Ampicillin
Rifampin
Trimethadione
Tiopronin
Tumors
Hodgkin disease
Lymphoma/leukemia
Solid tumors
Allergies
Food
Dust
Bee stings
Pollen
Poison ivy, poison oak
Dermatitis herpetiformis
<i>Data from references</i> [148] [162] [186] [187] [188] [823] [1224] [1225] [1226] [1227] [1228] [1229] [1230] [1231] .

change glomerulopathy may also occur with solid tumors as an apparent paraneoplastic phenomenon.

There is also an association of minimal change glomerulopathy with food allergy. This is an important association in that, in some patients, removal of the allergen has resulted in resolution of the proteinuria. In 42 patients with nonbiopsied idiopathic nephrotic syndrome, 16 had positive skin tests for food allergy. In 13 patients, an oligoantigenic

diet was prescribed, resulting in a significant reduction in proteinuria.^[150] Thus, it is important to ask patients about potential allergens, especially those found with food.

A syndrome of minimal change glomerulopathy accompanied by a reversible acute renal failure has a higher incidence in adults than in children.^{[146] [151] [152]} This syndrome of adult minimal change glomerulopathy with acute renal failure was studied in 21 patients who had a serum creatinine greater than 177 mmol/L on presentation, compared with 50 adult patients with minimal change glomerulopathy and a serum creatinine of less than 133 mmol/L. Patients who presented with acute renal failure were older (59 years vs. 40 years), had a higher systolic blood pressure (158 mm Hg vs. 138 mm Hg), and had more proteinuria (13.5 vs. 7.9 g/24 hours). Importantly, renal biopsy demonstrated evidence of atherosclerosis and focal tubular epithelial simplification compatible with ischemic acute renal failure. Of the 18 patients with renal failure for whom follow-up data were available, all had recovery of renal function, but some only after substantial dialytic support.^[114]

A review of 79 patients in the literature since 1966 revealed a similar finding in an older population with high urinary protein excretion, low serum albumin, and persistence of acute renal failure for up to 77 weeks. Histopathologic findings of acute tubular necrosis were found in 47(60%) of these patients.^[151] When treating older patients, it is important to recognize that acute renal failure may be present in the setting of minimal change glomerulopathy, and that dialytic therapy may be necessary to tide the patient over while corticosteroid treatment induces a response.

Laboratory Findings

The ubiquitous laboratory feature of minimal change glomerulopathy is severe proteinuria. Microscopic hematuria

is seen in fewer than 15% of patients, with only rare episodes of macroscopic hematuria. The rapidity of the development of proteinuria in some patients is associated with evidence of volume contraction with hematocrit and hemoglobin increased. The erythrocyte sedimentation rate is increased as a consequence of hyperfibrinogenemia as well as hypoalbuminemia. The serum albumin concentration is usually depressed, whereas the total cholesterol, LDL, and triglyceride levels are increased. Total serum protein concentration is usually reduced to between 4.5 and 5.5 g/dL with a serum albumin concentration of generally less than 2 g/dL and, in more severe cases, less than 1 g/dL.^[153] Pseudohyponatremia has been observed in the setting of marked hyperlipidemia. Serum calcium may be low, largely due to hypoproteinemia.

Several abnormalities that promote thrombosis occur frequently in patients with severe nephrosis, including increased plasma viscosity, increased red blood cell aggregation, low plasminogen, and low antithrombin III.^[11]

Renal function is usually normal, although the serum creatinine may be slightly increased at the time of presentation.^{[152] [154] [155]} A minority of patients (usually older adults) has substantial acute renal failure, as discussed earlier.

The loss of albumin into the urine is largely a function of a loss of charge-selective permselectivity.^{[156] [157] [158] [159]} Consequently, the fractional excretion of albumin is proportionately greater than the fractional excretion of IgG. IgG levels, however, may be profoundly decreased—a factor that occurs most notably during episodes of relapse. This low level of immunoglobulin may result in susceptibility to infections. IgM levels can be elevated after a remission.^[160] Mean serum IgA levels may be substantially elevated in patients with minimal change glomerulopathy compared to those with other renal disease^[161] and are also elevated in association with relapse in children.^[162] Among adult patients with minimal change glomerulopathy, over half have elevated levels of serum IgE and two thirds of patients have evidence of some allergic symptoms.^[163] Elevation of IgE suggests a relationship between minimal change glomerulopathy and allergy. Complement levels are typically normal in patients with minimal change glomerulopathy.

Treatment

The general approach to treatment of patients with minimal change glomerulopathy has been corticosteroid therapy. For children, the dose of prednisone is 60 mg/m² /day. For an adult, the dose of prednisone is 1 mg/kg body weight, not to exceed 80 mg/day. In children, this form of therapy results in a complete remission with disappearance of proteinuria in over 90% of patients within 4 to 6 weeks of therapy. A response to prednisone therapy has occurred if the patient has had no proteinuria by dipstick analysis for at least 3 days. It should be noted that the serum albumin and serum lipid levels might not return to normal for prolonged periods of time following resolution of proteinuria.^[164]

Treatment is generally continued for 6 weeks after there is complete remission of proteinuria. During those 6 weeks, the dose should be changed to alternate-day prednisone or to a stepped reduction in the daily dose of prednisone. If the dose is changed to alternate-day when remission has occurred, the dose may be decreased in children from 60 mg/m² /day to 40 mg/m² /day.^{[122] [165] [166] [167] [168] [169]} In adult patients with minimal change glomerulopathy, a response to corticosteroid treatment may take up to 15 weeks.^[146] In a study of 89 adult patients given prednisolone, 60% were in remission after 8 weeks, 76% after 16 weeks, and 81% over the course of the study. Of the 58 treated patients who responded, 24% never relapsed, 56% relapsed on a single occasion or infrequently, and only 21% were frequent relapsers. Of these 89 patients, only 4 remained nephrotic, and 2 of these presented with acute renal failure. Cyclophosphamide therapy was administered to 36 of the 89 patients, with 66% of these patients being in remission at 5 years.

One of the most controversial treatment issues pertains to the tapering regimen of prednisone after the initial response. Sudden withdrawal of corticosteroids, or a rapid taper of prednisone immediately following complete remission, may prompt a relapse. Whether this is a consequence of adrenal insufficiency or depression of the pituitary-adrenal axis has been a matter of debate.^{[169] [170] [171]} At least in children, the likelihood of

relapse is decreased with prolonged use of corticosteroids over a 10- to 12-week period.^{[167] [172] [173]} Once remission has been obtained, an alternate-day schedule should begin within at least 4 weeks of the response in order to decrease the steroid-induced side effects.

In children who have not been biopsied prior to treatment, a renal biopsy is usually appropriate when there is failure to respond to a 4- to 6-week course of prednisone, particularly if there have been changes in the clinical course during this period of time, suggestive of another glomerular disease. Many pediatricians advocate renal biopsy at the onset of the disease if there are clinical features suggesting a diagnosis other than minimal change glomerulopathy (e.g., hypertension, red blood cell casts in the urine, or hypocomplementemia), or if the nephrotic syndrome begins in the first year of life or after 6 years of age.

After the clinical response to initial treatment, as few as 25% of patients have a long-term remission,^[152] 25% to 30% have infrequent relapses (no more than one a year), and the remainder have frequent relapses, steroid dependency, or steroid resistance ([Table 28-9](#)). Frequently relapsing or steroid-dependent nephrotic patients require additional forms of therapy aimed at minimizing the complications of corticosteroid therapy. Generally, induction of a remission with prednisone therapy followed by institution of cyclophosphamide results in higher urine flow rates and reduced risk of

TABLE 28-9 -- Patterns of Response of Minimal Change Glomerulopathy to Corticosteroid Treatment
Primary responder, no relapse
Primary responder with only one relapse in the first 6 mo after initial response
Initial steroid response with two or more relapses within 6 mo (frequent relapse)
Initial steroid-induced remission with relapses during tapering of corticosteroid, or within 2 wk after their withdrawal (steroid-dependent)
Steroid-induced remission, but no response to subsequent relapse
No response to treatment (steroid-resistant)
<i>Data from references</i> ^{[167] [168] [183] [1189]} .

hemorrhagic cystitis. When cyclophosphamide is used in doses of 2 mg/kg for 8 to 12 weeks, 75% of patients remain free of proteinuria for at least 2 years.^{[140] [146] [174] [175]} The response to cyclophosphamide may be predicted from the response to corticosteroids. Patients who have an immediate relapse after cessation of corticosteroids will have a

greater chance of relapsing immediately after cessation of cyclophosphamide. Those who have longer remissions after corticosteroid therapy will have a decreased risk of relapse after cyclophosphamide.^[176] In steroid-dependent patients, the response to cyclophosphamide has been improved by increasing the duration of therapy to up to 12 weeks.^[174] In at least one other study, the 12-week course of cyclophosphamide has not proved efficacious.^[177]

Chlorambucil has many of the same toxicities as cyclophosphamide, and in children may be associated with a higher incidence of malignancy.^{[178] [179]} However, the use of chlorambucil at a dose of 0.1 to 0.2 mg/kg/day in an 8-week course may produce more stable remission than cyclophosphamide^{[180] [181]} and has been reported to be effective in some cyclophosphamide-resistant children.^[182] Both cyclophosphamide and chlorambucil have profound side effects that include life-threatening infection, gonadal dysfunction, hemorrhagic cystitis, bone marrow suppression, and potential mutagenic events. The disadvantage of chlorambucil is the inherent higher risk of leukemia than with cyclophosphamide.^[149]

In patients unresponsive to an alkylating agent but who have a predictable response to corticosteroid therapy, the challenge becomes how best to decrease major complications associated with prolonged and repetitive bouts of corticosteroid therapy. In addition to the development of life-threatening infections, prolonged corticosteroid therapy may lead to osteoporosis, diabetes mellitus, and accelerated atherosclerosis. Many patients have profound mental status changes, especially emotional lability, with intermittent corticosteroid treatment. In patients unresponsive to alkylating therapy, the question is whether other forms of therapy are indicated. Notably, end-stage renal failure is rare in minimal change glomerulopathy. In light of these considerations, additional forms of therapy must be considered carefully with respect to the cumulative addition of other immunosuppressive drugs.

Steroid-Resistant Minimal Change Glomerulopathy

Approximately 5% of children with minimal change glomerulopathy appear to be steroid-resistant. In nonbiopsied patients, resistance to corticosteroid therapy is an indication for renal biopsy. Often, the renal biopsy evaluation will demonstrate focal segmental glomerulosclerosis or forms of glomerular injury other than minimal change glomerulopathy.^[183]

If the diagnosis remains minimal change glomerulopathy after renal biopsy evaluation, there may be several reasons for steroid resistance. Some patients, especially those for whom corticosteroid therapy is overly toxic, may skip doses or not fully comply with therapy. In other patients, especially adults, alternate-day therapy may not provide sufficient amounts of corticosteroid to induce clinical remission. In very edematous patients, oral corticosteroid therapy may not be well absorbed, and a dose of intravenous methylprednisolone may provide a more reliable route of administration. Available data suggest that pulse methylprednisolone may induce remission in some corticosteroid-resistant children. In one study, five of eight corticosteroid-resistant children had a remission with pulse methylprednisolone,^[184] although this experience is not universal.^[185]

Cyclosporine can be administered at a dose of approximately 5 mg/kg. Up to 90% of patients may have either partial or complete remission with cyclosporine.^{[162] [167] [186] [187] [188]} Unfortunately, patients who experience long-term remission once cyclosporine is discontinued are rare.^[168] Two trials examined the use of cyclosporine in steroid-resistant nephrosis. The French Society of Pediatric Nephrology used cyclosporine with prednisone at a dose of 30 mg/m² /day for the first month, and then alternate-day prednisone for 5 months. Cyclosporine was administered at a dose of 150 to 200 mg/m² /day.^[189] In this study, 48% of patients with minimal change glomerulopathy had complete remission, some within the first month of therapy. A minority of the responders became steroid-sensitive when they later relapsed. In a study by Ponticelli and colleagues,^[190] 13 of 45 patients had minimal change glomerulopathy and were treated with cyclosporine. In patients with minimal change glomerulopathy, partial or complete remission occurred within 2 months of beginning therapy. Unfortunately, the early positive results of this study were associated with relapses in all patients after cyclosporine was stopped.

In a summary of nine studies,^[191] only 20% of children had complete remission with cyclosporine, and many, if not most, relapsed upon cessation of therapy. Moreover, cyclosporine and cyclophosphamide appear to have a similar degree of efficacy in controlling the nephrotic syndrome, but cyclophosphamide-treated patients have more stable long-term remission.^[192] In this study, the likelihood of a long-term remission in patients treated with cyclophosphamide was 63%, and was only 25% in those treated with cyclosporine.

To counteract the common relapse of nephrosis when cyclosporine has been used for 6 months, an alternative approach to cyclosporine treatment relies on a long-term course of this drug, using gradually lower doses to maintain remission. In one study,^[193] patients in complete remission for more than 1 year on cyclosporine remained in remission if the cyclosporine was gradually tapered and then stopped. Repeat biopsy in this patient population treated for as long as 20 months showed no overt sign of nephrotoxicity.

Levamisole is an antihelmintic that also has an immunostimulating role.^{[189] [194]} A typical dose is 2.5 mg/kg body weight given orally on alternate days or three times per week. In one study, 61 children were given a 3- to 4-month course of placebo or levamisole after remission of proteinuria was induced by corticosteroids. In that study, 14 of 31 patients using levamisole discontinued steroid therapy and remained in remission, compared with only 4 of 30 control subjects.^[194] Moreover, when levamisole was administered to patients after a steroid-induced remission, relapse was substantially decreased from 5.2 episodes to less than 0.7 episode per year during 24 months of treatment.^[195] The side effects of this drug, at least in children, include transient cytopenia in two thirds of patients. More profound complications have been reported in treatment with