Review Article

Minimal Change Disease: A Review

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Abstract: Minimal change disease (MCD) is a histopathological lesion in the kidney that is most commonly associated with nephrotic syndrome. The majority of the cases are idiopathic. Pathogenesis is not well understood, although T-cell-related mechanisms are implicated. Massive proteinuria leads to hypoalbuminemia, salt retention, disorder of hemostasis, hyperlipidemia and increased susceptibility to infections. Renal biopsy remains the gold standard for diagnosis. MCD is highly responsive to corticosteroids. Other immunosuppressive agents such as cyclophosphamide, cyclosporin, azathioprine and mycophenolate mofetil have been used to treat cases which are resistant to steroids.

Key Words: minimal change disease, nephrotic syndrome, proteinuria

Minimal change disease was first described as lipoid nephrosis.[1] Other terms previously used to describe this disease also include Nil disease, steroid-sensitive nephrotic syndrome, steroid-responsive nephrotic syndrome and idiopathic nephrotic syndrome. The term lipoid nephrosis was used to describe the finding of lipids in the renal tubular cells as well as lipid-laden proximal tubular cells or macrophages known as oval fat bodies in the urine. Nil disease refers to the presence of little or no inflammatory changes in the glomerulus by light microscopy. It is called idiopathic nephrotic syndrome due to the fact that there is no association with glomerulonephritis or systemic diseases such as diabetes or amyloidosis.

The glomerulus, a portion of the nephron, is composed of a delicate capillary network. This network is lined by a thin layer of endothelial cells, mesangial cells, and epithelial cells with their basement membrane. The mesangial cells are surrounded by a mesangial matrix. When a disease affects the glomerulus, nephrotic syndrome often results. This syndrome is associated with hypercoaguable state, hyperlipidemia, hypoalbuminemia, and several other effects. Minimal change disease (MCD) is one such disease that results in glomerular injury.

Epidemiology

This glomerular nephropathy is most often seen in children, but is also responsible for 15% of the adult cases of idiopathic nephrotic syndrome. It is more commonly seen in males with an equal incidence in adolescents.[2] The incidence varies geographically and is reported to be as low as 1 per million in the US. It is more common in Asia than North America or Europe.[3]

Clinical Features

Facial edema is typically noted first, but scrotal and vulval edema may be more pronounced as the disease progresses. Pleural and ascitic fluid accumulation may be severe enough to give respiratory distress. Dependent edema is the most common finding. Unlike the other types of glomerulonephritis, the blood pressure is usually normal, but can be elevated in the adult population.[4] The retina has a characteristic wet appearance. Subungual edema may reverse the normal fingernail color pattern such that the white lunulae may be pink and the rest of the nail bed white. Muehrcke lines, which are horizontal white lines in both the fingernails and toenails, may also be seen.

Vague symptoms of headache, irritability, fatigue, malaise, and depression are common. Hematuria is rare in minimal change disease.

Etiology

The majority of cases of MCD are primary or idiopathic. Often there is no precipitating cause, but sometimes the de-

Key Points

- Minimal change disease presents as nephrotic syndrome.
- T-cell-related mechanisms are implicated in pathogenesis.
- Renal biopsy is the gold standard for diagnosis.
- Patients may be prone to hypercoagulable state.
- Steroids and other immunosuppressive-based regimens are used for treatment.

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velopment of edema and proteinuria are preceded by upper respiratory infections, allergic reactions to bee stings, and use of certain drugs such as nonsteroidal anti-inflammatory drugs (NSAIDs). MCD is commonly seen among elderly females with a long history of NSAID use. They usually have nephrotic-range proteinuria and occasionally present with acute renal failure. Complete remission is usually seen after cessation of NSAIDs.[5] Additional ingestions associated with MCD include gold, penicillamine, ampicillin, and mercury.[6–9] Malignancy such as Hodgkin disease is occasionally associated with MCD in adults as well as children. One literature review revealed that minimal change disease was found in 33 of 134 cases of cancer-related nephrotic syndrome. Twenty-six of those patients with MCD had Hodgkin disease.[10,11] Other malignant conditions associated with minimal change disease are leukemia and non-Hodgkin lymphoma.

Pathogenesis

The pathogenic mechanism of MCD is not well understood. It has been proposed that T-cells are responsible. T-cells are thought to release several cytokines which injure the glomerulus. In one study, T-cell subsets were measured in steroid-responsive nephritic syndrome.[12] During the time of disease relapse, CD8 lymphocytes were increased and CD4 lymphocytes decreased. The decrease in CD4 lymphocytes could be secondary to prednisone; however, the increase in CD8 lymphocytes strongly suggests the involvement of T-cell subsets in the pathogenesis of MCD. Studies suggest that T-cell hybridomas derived from the T-cells of patients with MCD produce a molecule known as glomerular permeability factor (GPF). This permeability factor induces significant proteinuria when injected into rats. The molecular weight of GPF and its tumor necrosis-like activity suggest that GPF may be a lymphokine.[13] Some investigators believe that GPF is produced by the T-cells which mediate abnormal glomerular permeability; others propose that GPF is similar to human plasma glycoprotein hemopexin which is an acute phase reactant. Alternate perfusion in the rat kidney showed that both GPF and hemopexin cause significant enhancement of urinary protein leakage through the glomerular basement membrane.[14] GPF may also be associated with the recurrence of nephrotic syndrome after renal transplantation. It is not clear whether this is the same permeability factor which causes recurrence of focal segmental glomerulosclerosis (FSGS) in posttransplant patients. However a possible link between abnormal T cell response and glomerular disease was described 30 years ago. Hoyer and associates first described early recurrences of steroid responsive nephrotic syndrome after renal transplantation. Subsequently Maucer et al described a similar case of recurrent steroid responsive nephrotic syndrome in a 2-year-old renal transplant recipient. These reports are consistent with persistence or recurrence of circulating factor produced by T cells in such recipients. A reverse study was published in 1994 where MCNS kidneys had been transplanted into 2 recipients and features of MCNS resolved completely post transplant.[15–17]

Serum immunoglobulins have also been measured in patients with MCD and other chronic glomerular diseases.[18] Both IgA and IgG were reduced in MCD and chronic glomerular disease. Although the absolute number increased with treatment, the mean value remained low. IgM levels were increased in both groups, but the elevation was significantly higher in MCD. This finding suggests that the abnormal pattern of immunoglobulins seen in MCD and other glomerular diseases is not merely due to a urinary loss of immunoglobulins, but an inability to convert from IgM to IgG or IgA during immune system stimulation. This inability is felt to be due to a selective deficiency in thymic cell function.

Mechanism of Proteinuria

Most of the abnormalities observed in primary nephrotic syndrome are directly or indirectly related to proteinuria. One liter of plasma contains 60 to 80 g of protein, but normal protein excretion in the urine is less than 150 mg/d. This demonstrates the extraordinary capability of the renal filtration mechanism to retain protein. The filtration barrier of the glomerular capillary bed consists of three layers, with the first being fenestrated endothelium. The fenestrae are about 70 nm in diameter. Therefore, this is a minimal barrier for smaller proteins like albumin which is only 3.6 nm. The second layer is the glomerular basement membrane (GBM) which is a filtration barrier by virtue of negative charge. The GBM is a trilaminar membrane consisting of fibronectin, laminin, type IV collagen, and negatively charged heparan sulfate proteoglycans. The last layer of the glomerular capillary bed is the epithelial cells. The epithelium is not a continuous layer but rather an interdigiting extension from the adjacent epithelial cells or podocytes separated by spaces which form narrow slits, through which filtrate passes. The surface of the adjacent foot processes are coated by negatively charged sialoproteins believed to be the main barrier for the filtration of plasma proteins. Perfusion of the rat kidney with polycationic substances such as protamine sulfate may lead to neutralization of the negative charge and can cause massive proteinuria.

Physiologic studies suggest that the glomerulus has size selective properties as well. Restriction to filtration increases with increasing molecular size. Electrostatic charge also modifies the movement of macromolecules across the glomerulus. Negative charges in the endothelium, glomerular basement membrane, and epithelium are collectively known as polyanions. This allows the facilitated transport of glomerular polycations and restricts the transport of polyanions.[19]

To understand the mechanism of proteinuria in MCD, renal handling of albumin and neutral dextrans was studied in 7 MCD patients.[20] It was found that although albumin excretion was greatly increased, the fractional excretion of dextran

was reduced in comparison to healthy volunteers. This suggests that mean glomerular pore size is decreased in MCD. Increased excretion of albumin indicates that loss of glomerular charge selectivity is the main mechanism of proteinuria in MCD.

Consequences of Proteinuria

Hypoalbuminemia

Low serum albumin results from an increase in urinary loss and increased catabolism of protein. Although there is increased hepatic synthesis of albumin, it is inadequate to compensate for the urinary losses.[21]

Salt Retention

Retention of sodium is a well-established fact in nephrotic patients. Hypoalbuminemia reduces the plasma oncotic pressure. This results in the translocation of fluid from the vascular to the interstitial space which leads to hypovolemia. Hypovolemia in turn stimulates the renin-aldosterone system which leads to increased sodium reabsorption. However, the renin-aldosterone system is not the only mechanism of sodium retention in the nephrotic patient. Another proposed mechanism is the inability of the nephrotic kidney to excrete sodium. This could be related to a decreased sensitivity to atrial natriuretic peptide (ANP) and subsequent sodium retention.[22] ANP causes renal vasodilation, increased GFR, decreased sodium chloride reabsorption in the distal nephron and inhibited renin secretion. Renal handling of sodium was studied in 23 children at different stages of MCD.[23] Absolute and fractional basal sodium excretion was significantly reduced in the edema-forming stage when compared with the proteinuric steady state and the remission stage. In contrast to proteinuric patients in steady state and nonproteinuric patients, edematous patients failed to respond to isotonic saline infusion by increasing sodium excretion. However, the plasma aldosterone level was normal in 11 of 14 proteinuric patients and did not correlate with basal sodium excretion.

Disorder of Hemostasis

Patients with nephrotic syndrome are at high risk for thromboembolic events as well as renal vein thrombosis. The prevalence of thromboembolic complications is higher in adults than children with venous thrombosis being more common than arterial. A hypercoaguable state may develop in minimal change disease for the following reasons: (a) increased platelet aggregation secondary to thrombocytosis and release of beta thromboglobulin for platelets; (b) increased procoagulant activity secondary to physical conditions of the nephrosis such as hemoconcentration and hyperviscosity; (c) increased production of factor V and factor VIII due to excessive urinary loss of protein S; (d) reduction of antithrombin III, which inhibits thrombin; and (e) hypertriglyceridemia can also lead to a hypercoaguable state.

Effects on Lipids

Hyperlipidemia is a significant problem in nephrotic syndrome. Increased lipoprotein synthesis in nephrotic syndrome is a secondary phenomenon due to hypoalbuminemia. A daily infusion of albumin has been shown to raise serum albumin levels and subsequently decrease serum lipid levels.[21]

Infection

Increased susceptibility to infection in MCD is secondary to a decrease in the ability to generate specific antibodies as well as loss of antibodies in the urine. This may be potentiated by the prolonged presence of gross edema or ascitic fluid which are ideal medias for bacterial growth. Moreover, therapy with steroids or other immunosuppressive drugs further increases the risk of infection. In addition, a decreased serum level of alternative complement pathway factor B results in defective opsonization of *E. Coli* and defective neutrophil function in nephrotic syndrome. The level of this factor strongly correlates with the serum albumin level.[24]

Thyroid Function

In nephrotic syndrome, there is usually a urinary loss of thyroid-binding globulin (TBG), T3, and T4. This results in a decreased serum level of T3 and T4. However, free T4 and TSH remain normal and most of the patients are euthyroid. The urinary loss of TBG correlates with total urinary protein.[25]

Metabolism of Calcium and Other Minerals

Even though levels are decreased, there is skeletal resistance to PTH secondary to vitamin D deficiency.[26] An alteration in metabolism of trace elements may be due to the actual loss of the metal or its carrier protein. There are reports of decreased serum levels of iron and copper associated with low serum iron binding capacity and low erythrocyte copper content. Copper in the plasma is bound exclusively to alfa-2 globulin which is also known as transferrin. These two metals are excreted in large quantities in the urine of patients with pronounced proteinuria. If this loss continues, the capacity of the body to synthesize these elements will lag behind the loss resulting in decreased serum levels. IV administration of albumin has been shown to increase albuminuria and increase metal excretion. Severe iron deficiency may cause a microcytic, hypochromic anemia and copper deficiency can give rise to a similar type of anemia as well. This anemia usually does not respond to administration of iron or copper.[27–29] Zinc deficiency in patients with nephrotic syndrome could also be related to increased urinary losses of binding protein.[30]

Effects on Drugs

The serum level and resulting toxicity of protein-bound drugs may increase in nephrotic patients due to the proteinuria. For example, digoxin, digitoxin and hydrochlorothiazide (HCTZ) are 25%, 90% and 60% bound to plasma proteins, respectively. The dose of these drugs needs to be adjusted in the setting of proteinuria to avoid toxicity.

Diagnosis

Renal biopsy remains the gold standard for diagnosis in adults. However, in children, a biopsy is likely performed only in certain circumstances. For example, if the patient fails to respond to a 4-week trial of prednisone therapy or is younger than age 1 or older than age 6 at presentation. Biopsy is also considered if the clinical course changes and features of glomerulonephritis become evident.

Histopathology

The histopathological appearance of minimal change disease by light microscopy is completely normal. The visceral epithelial cell of the glomerulus is the main target cell in MCD. The loss of epithelial foot processes is the only abnormality seen by electron microscopy in MCD. The slit-pore membranes that bridge the space between adjacent foot processes of podocytes are nearly always obliterated. Nephrin, an important component of the slit-pore membrane, was found to be reduced in patients with MCD.[31] Dystroglycan, an adhesion protein which anchors and stabilizes podocytes in the glomerular basement membrane was found to be reduced in MCDS whereas it was not different in normal kidney and in patients with FSGS.[32] Immunofluorescence technique does not show any immunoglobulin or complement deposition in MCD. However, immunoglobulin M staining and mesangial proliferation has been described by some investigators. Some studies indicate that mesangial proliferation and/or staining with IgM are variants of minimal change disease, but not all studies agree. Although deposition of IgM does not appear to affect the prognosis of the disease, mesangial hypercellularity usually is associated with poor response and frequent relapse.[33]

Minimal Change Disease and Focal Segmental Glomerulosclerosis

It is still controversial as to whether MCD and focal segmental glomerulosclerosis (FSGS) are different diseases or a spectrum presentation of the same disease process. This is due in part to similarities of clinical presentations as well as immunofluorescence and ultrastructural findings. However, the differences in the response to steroid therapy suggest that MCD and FSGS are indeed different disease entities. It has been shown that some cases of MCD progressively develop into FSGS.[34] In these cases, it has been suggested that FSGS was missed in an early biopsy due to a sampling error, or the fact that no juxtamedullary glomeruli were identified for evaluation. Both MCD and FSGS can occur with or without mesangial proliferation. Opinion varies regarding the mechanism of MCD progression into FSGS. The most widely accepted theory is that glomerulosclerosis results from a continuous loss of large amounts of protein across the GBM or directly into the mesangium.

Acute Renal Failure

Acute renal failure in minimal change disease is uncommon. Hypovolemia, exposure to contrast media, NSAID use, and allergic interstitial nephritis either alone or in combination may precede the development of acute renal failure. Several studies have shown that MCD patients with acute renal failure are usually older, have higher systolic blood pressures, and have more arteriosclerotic changes involving the intrarenal artery at renal biopsy. It has been proposed that preexisting arteriolar narrowing and hypertension in a nephrotic individual may directly or indirectly increase renin release leading to ischemia and tubular injury. It has also been shown that severe interstitial edema may lead to renal failure by predisposing tubular collapse. Treatment with diuretics may improve renal function in some cases.[35–36]

Treatment

Several studies which have included a large number of children with minimal change are available in the literature. Treatment recommendations have been made based on these trials. However, very few adult patients with MCD were included in these studies. Therefore, the lack of sufficient data makes it difficult to make any clear treatment recommendations in this subset of patients. Salt and water retention is a common phenomenon in patients with nephrotic syndrome, making a low-salt diet and diuretics helpful. IV albumin has been used with loop diuretics in patients with intractable edema and severe hypoalbuminemia. However, some studies show that patients treated with albumin have an increased risk of relapse.[38] The effect of water immersion has been studied in patients with nephrotic syndrome. Water immersion provides a potent natriuretic impulse due to redistribution of blood volume with relative hypervolemia.[39]

Treatment of First Attack

The first line of therapy for MCD is steroids. Since MCD is exquisitely sensitive to steroid treatment, the disappearance of proteinuria in children is considered diagnostic for MCD. Treatment recommendations for the first attack of MCD in children is 2 mg/kg/d of prednisone (not to exceed 60 mg/d) for 6 to 8 weeks. Due to the lower incidence of complete remission and slower response to therapy, the duration of treatment in adults can be extended up to 16 weeks. A dose of 1 mg/kg/d is commonly used for adults.[40–44]

The clinical course of MCD can be described based on

response to steroid treatment. Complete remission is defined by the absence of proteinuria by dipstick for at least 3 days. Partial remission is reduction of proteinuria from a previous level. Recurrence of proteinuria for at least 3 consecutive days is defined as a relapse. The frequency of steroid therapy should be reduced to every other day once complete remission of proteinuria is achieved. This should be continued for several weeks and then tapered slowly over the course of several months. Studies indicate that complete remission occurs within 8 weeks in 93% of children with MCD. In adults, complete remission is achieved only in 51 to 76% in 8 weeks and 76 to 96% in 16 weeks.[42–44]

Treatment of Steroid Resistant and Frequently Relapsing MCD

Optimal therapy for frequent relapsers is not clear because of the lack of large studies comparing different treatment modalities. However, a number of immunosuppressant medications have been tried including alkylating agents such as cyclophosphamide 2 mg/kg/d or chlorambucil 0.15 mg/kg/d with tapering alternate day prednisone for 8 weeks. These have been shown to achieve a remission rate of 63% at 10 years follow up. Various serious side effects restrict their use in the frequent relapsers. The side effects of cyclophosphamide include bone marrow suppression leading to infection, anemia, hemorrhagic cystitis, bladder cancer, infertility, and secondary malignancy such as leukemia. Chlorambucil may have a higher risk of malignancy than cyclophosphamide.

The treatment of choice for steroid-dependent MCD (relapse during steroid taper) is cyclophosphamide 2 mg/kg/d for 8 weeks or cyclosporine 6 mg/kg/d for children and 5 mg/kg/d for adults for 6 to 12 months. Optimal duration of therapy is unknown. Prolonging the treatment of cyclophosphamide to 12 weeks did not show any benefit.[45,47] Although cyclosporin, mycophenolate, azathioprine, and levamisole are less toxic than cyclophosphamide, the rates of remission and subsequent relapse rates with these agents are less favorable when compared with cyclophosphamide. Patients with MCD experience more prolonged remissions than patients with FSGS after treatment with cyclophosphamide.[46] These medications are important not only because of their efficacy for the underlying disease but also because they are steroid sparing. This may allow the avoidance of the side effects of steroid therapy including infection, diabetes, hypertension, acne, striae, Cushingoid face, osteopenia, osteoporosis, avascular necrosis, and psychiatric changes.

Cyclosporin has been shown to be helpful in steroid-resistant nephrotic syndrome as well. Efficacy and safety of cyclosporin was compared with supportive therapy in this patient population.[48] Forty-five patients with steroid-resistant idiopathic nephrotic syndrome were assigned to supportive therapy or cyclosporin (5 mg/kg/d in adults and 6 mg/kg/d in children) for 6 months. The dose of cyclosporin was gradually tapered by approximately 25% every 2 months until complete discontinuation. During the first year, 13 of the 22 cyclosporin-treated patients versus 3 of the 19 control patients achieved complete remission. The response is higher in steroid-responsive and steroid-dependent patients, but 60% of steroid-resistant patients also responded to cyclosporin therapy. When comparing remission periods, cyclophosphamide-treated patients had a stable, longer remission than cyclosporin-treated patients. One report showed that 26 of 35 cyclosporin-treated patients and 18 of 28 cyclophosphamide-treated patients achieved complete remission.[49] A follow-up report indicated that at 2 years, 25% of the patients treated with cyclosporin (50% adult and 20% children) and 63% of those given cyclophosphamide had not experienced relapse. The higher likelihood of prolonged remission and the lower cost of cyclophosphamide when compared with cyclosporin makes it the regimen of choice for steroid-dependent and frequently relapsing MCD. It is important to remember that cyclosporin is safer than repeated courses of cyclophosphamide.

Levamisole, an antihelminthic agent, although no longer available in the US, has been used alone or in combination when patients are dependent on high-dose steroids or alkylating agents and fail to maintain remission. One such study described 61 children with frequently relapsing steroid-dependent nephrotic syndrome who were randomly assigned to alternate day levamisole 2.5 mg/kg or placebo for a maximum of 112 days.[50] Fourteen patients in the levamisole group and 4 in the placebo group remained in remission at 112 days. Steroids were gradually reduced and stopped at Day 56. No significant side effects such as neutropenia, rash, or liver toxicity were observed. However, like cyclosporin, continuous treatment is required to get maximum benefit. Discontinuation of levamisole led to the relapse of proteinuria in 10 of 14 patients within 3 months. Only 4 were in remission at the end of the study. It is not clear whether increasing the duration of treatment may result in better outcomes.

Azathioprine has been used in patients with MCD. Some earlier studies failed to show any benefit when compared with placebo. A recently performed uncontrolled trial showed that all the 13 patients with steroid-resistant nephrotic syndrome treated with azathioprine went into remission.[51]

There is limited experience with mycophenolate mofetil. However, a recent study described 46 patients with primary glomerulopathies who received mycophenolate for over 3 months as adjunctive or primary treatment. The majority of the patients tolerated the drug without hematological, hepatic, or other side effects. Substantial improvement in proteinuria and stabilization of serum creatinine was seen.[52,53]

Prognosis

The prognosis of MCD is better in children than adults. At least 70% of children with MCD enter adult life without renal injury or urinary abnormalities. In contrast, a much less favorable outcome is expected if the nephrotic syndrome is

associated with FSGS or membranous proliferative glomerulonephritis (MPGN). Adults with MCD also have a good prognosis, with more than 90% surviving 10 years or more without the development of end-stage renal disease. Although adults with MCD resemble children in many respects, they go into acute renal failure more frequently and are more likely to have hypertension and diminished renal function. Adults respond slower and slightly less often to both steroids and cytotoxic agents but relapse less frequently and have more stable remissions after cyclophosphamide treatment.[54] When compared with adults with FSGS, patients with MCD have better prognosis.

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Erratum

We regret that there was a statistical error in the September issue of the *Southern Medical Journal*. In the article titled "Adult Health Screening and Referral in the Emergency Department," by Drs. Zun and Downey, the number of referrals for Pap smears was listed as 2.6% (39 of 157 patients). The correct numbers are as follows:

Patients eligible for Pap smear 113: (50.9%)
Number of patients who had a Pap smear within the last year: 74 (33.3%)
Number of patients who needed a Pap smear: 39 (17.6%)
Followup with Pap smear?
- Yes: 4 (1.8%)
- No: 15 (6.8%)
- Unknown: 19 (8.6%)
- Not needed: 183 (82.8%)

Pap follow up confirmed:
- Yes: 18 (8.1%)
- No: 4 (1.8%)
- Unable to find patient: 13 (5.9%)