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Review Article

Minimal change disease

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ABSTRACT

Minimal change disease is the commonest cause of nephrotic syndrome in children and third most common cause in adults. There are new insights in the pathogenesis of disease, and it is now considered a podocyte disorder. New biomarkers have been identified to explain the pathogenesis. The treatment in children is almost standardised, however in adults, the evidence is not so robust and treatment is mostly extrapolated from randomized trials in children and uncontrolled or retrospective studies in adults. The long term prognosis of disease is excellent in children and steroid sensitive patients. Steroid resistance is a marker of poor prognosis. Genetic studies are helpful in detecting patients with mutations, as, they do not respond to immunosuppressive drugs. The therapeutic armamentarium of treatment of MCD has widened with discovery of new immunosuppressive drugs like tacrolimus, mycophenolate mofetil and rituximab, which are helpful in treatment of steroids resistant and steroid dependent nephrotic syndrome.

1. Introduction

Minimal change disease (MCD) or minimal change nephrotic syndrome (MCNS) is the most common cause of idiopathic nephrotic syndrome in children.[1–3] It was first described in 1913 by Monk who called it 'lipoid nephrosis' because of lipids in tubular epithelial cells and urine.

As the name suggests MCD is characterised by either minimal, no abnormality or mesangial prominence in kidney biopsy in light microscopy and no or minimal immune deposits (low level of C3 and IgM) in immunofluorescence. The diagnosis is confirmed by diffuse foot process loss seen by electron microscope (EM).[2,3] The long term prognosis is very good in children.

2. Epidemiology

Minimal change disease is more common in Asia than in North America and Europe and rare in Africa. The incidence of MCD in America is 16 cases per million. There is a male preponderance of disease in children, where male to female ratio is 2:1 in some series.[1,2] The ISKDC study, which is the largest multicentre study of biopsy proven childhood nephrotic syndrome in children analysed 471 children between ages of 3 months to 16 years, and found that 363 (77%) of them had MCD as cause of nephrotic syndrome followed by FSGS in 37 (7.9%), membranoproliferative glomerulonephritis in 6.2% and rest in 8.8% of patients. MCD is more common between ages of 2–6 years (90–95%). After the age of 6 years, it is seen in about 65% of

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children and in only 20% of children <1 year of age.[3] In adults, MCD is the third most common cause of idiopathic nephrotic syndrome (10–15%), after membranous nephropathy (30–40%) and focal segmental glomerulosclerosis (20–30%).[4–6]

3. Pathogenesis

The pathogenesis of MCD is not fully understood till now. In the initial studies, Shalhoub proposed that the cause of lipoid nephrosis is abnormal regulation of T cell subset with T cell secreted circulating factor that damages the glomerular basement membrane and increases its permeability to protein. The explanations given were-response to glucocorticoids, remission in nephrotic syndrome by measles and presence of disease in some patients with Hodgkin's lymphoma (all of which alters cell mediated immunity) and when this circulating factor is removed from kidney, it functions normally. This is supported by the observation that transplantation of kidney from a patient of resistant MCD resulted in disappearance of proteinuria.[7] This hypothesis was accepted initially, but later on with new research in this field, this does not holds true. Newer studies have put emphasis on role of immune dysregulation in MCD. T-regulatory (Treg) cells, which attenuate immune responses by suppression of T-effector cells, are dysfunctional in humans with MCD, and it has been seen that augmentation of Treg cell function has led to decreased proteinuria in a rat model of the idiopathic NS.[7–11] In addition to these mechanisms, the roles of two podocyte proteins i.e.: CD80 and angiopoietin-like protein 4 (Angptl4) have been explored in patients with MCD.[12,13]

CD80 (also known as B7–1) is a transmembrane protein that is present on antigen-presenting cells and acts as a costimulatory signal for T cell activation. CD80 is also present in the podocytes of mice in MCD models and is necessary for development of proteinuria. Soluble urinary CD80 levels are elevated in children and adolescents with MCD in relapse compared with those individuals in remission, patients with other glomerular disease, and control subjects. Thus, CD80 may be a useful biomarker in MCD.[12] Angptl4 is another molecule, which has been studied in animal models of MCD. Angplt4 is a secreted glycoprotein that is present normally in podocytes at low levels, however it is highly upregulated in the glomeruli of several models of podocyte injury in rats, including puromycin aminoglycoside nephropathy (PAN). This upregulation is specific to models of steroid sensitive NS compared with models of membranous nephropathy, mesangial injury (Thy1.1 nephritis), and collapsing FSGS. Moreover, a transgenic mouse model showed that rats which have high plasma levels of Angplt4 do not have proteinuria, the proteinuria occurs only in NPHS2 – Angplt4 transgenic rats which overproduce Angplt4 specifically from podocyte. These rats develop many features of MCD i.e. loss of GBM charge, selectivity and response to glucocorticoids.[13] Another recent marker for MCD is interleukin 13 (IL-13). The rats expressing IL-13 develop minimal change disease.

4. Clinical presentation

Minimal change disease in children presents as nephrotic range proteinuria, which is defined as proteinuria >40 mg/m^2/h or >2 g/day, accompanied by hypoalbuminemia (serum albumin <2.5 g) and hypercholesterolemia.[1,2,22] In children the presentation is usually abrupt. Clinically it can manifest as facial swelling or periorbital edema. However sometimes children can present as anasarca, ascites and pleural effusion. The hypertension and hematuria is uncommon in children and if present due to MCD, it usually improves with improvement in nephrotic syndrome. Diastolic hypertension was seen in 13% of children in ISKDC study and microscopic hematuria is seen in <15% of children with MCD.[3] Occasionally some children might present with infections like cellulitis, peritonitis and pneumonitis.

In adults, nephrotic range proteinuria is defined as proteinuria of more than 3.5 gm/day. The clinical presentation is also different with presence of hypertension in 35–40%, acute renal failure (ARF) in 18–33%, microscopic hematuria in 28–47% and hypercholesterolemia in 96% of patients.[4–6] Patients who develop ARF are more likely to be male, hypertensive, older, have lower serum albumin and higher proteinuria as compared to those without ARF. The most common biopsy finding in these patients were acute tubular necrosis (ATN) followed by acute interstitial nephritis (AIN).[51,52] Kidney biopsy is essential for the diagnosis in adults.

5. Secondary causes of MCD

Although, MCD is usually idiopathic, however sometimes some other diseases or factors may lead to MCD.[1,2,14] The important secondary causes are-certain neoplasm, infections, drugs, and atopy.

5.1. *Neoplasm*

MCD can be associated with many neoplasms. The most frequent association has been found with Hodgkin's and non-Hodgkin's lymphoma. The MCD can precede or follow the occurrence of neoplasia by months to years. The casual association has been established as improvement in lymphoma lead to remission of nephrotic syndrome. The MCD may occur with many solid tumors as paraneoplastic syndrome. The malignancy in patient with MCD should be suspected, if patient has weight loss, anorexia, fever, lymphadenopathy, skin lesions, hematuria and pleural effusion etc. However the overall occurrence of MCD in patients with neoplasia is quite uncommon.

5.2. *Drugs*

Many drugs are found to be associated with MCD. The most common drugs are nonsteroidal anti inflammatory drugs (NSAIDs) especially fenoprofen. The patients with NSAIDs induced MCD also have renal dysfunction and kidney biopsy in these patients reveals changes of acute interstitial nephritis (AIN). These patients present clinically as rapidly progressive renal failure and nephrotic syndrome. Other important drugs are-lithium, penicillamine, gold, rifampicin, trimethadone, interferon, penicillamine etc. The drugs cause MCD by hypersensitive reaction or direct toxicity. Nephrotic syndrome in these patients usually resolves after discontinuation of offending agent. Steroids hasten the renal recovery in patients