# Membranous Nephropathy: Unpredictable Course and Controversial Therapeutic Approaches

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Membranous nephropathy (MN) is a challenge to nephrologists. It is the most common cause of nephrotic syndrome in adults and the second or third most common cause of end-stage renal disease (ESRD) within the group of primary glomerulonephritis (1). In adults, about 70-75% of cases are primary (idiopathic) and 25-30% are secondary to a variety of causes, including infections, neoplasm, SLE and other autoimmune diseases, drugs, diabetes (2, 3). MN in association with renal amyloidosis has also been found (4). The first step whenever the diagnosis of MN is made by renal biopsy is to recognise whether the disease is idiopathic or secondary, because they have different pathogenesis, treatment and prognosis. Idiopathic membranous nephropathy (IMN) is in situ immune complex disease. In secondary MN "planted" antigens may become trapped within the glomerulus: drugs, lectins and infectious agents. Circulating immune complexes have been implicated in the pathogenesis of tumour-antigen associated membranous nephropathy.

IMN is a non-proliferative glomerulonephritis. The in situ immune complex deposition results in gradual thickening of the capillary wall by new basement membrane synthesis. In Heymann's nephritis, rat model of human MN, an antigen has been identified as megalin, a 330 kD glycoprotein which is localized on visceral epithelial cells and proximal tubule brush border. Antibody binding to megalin results in alternative pathway complement activation with subsequent shedding of the immune complexes from the cell surface into the subepithelial space. No cellular infiltrates are seen on light microscopy, most likely because the immune deposits are not in direct contact with circulating immune cells. However, they can interact with soluble mediators to initiate an inflammatory response. The complement membrane-attack complex (MAC, C5b-9) can initiate glomerular capillary wall damage that results in proteinuria. Down-regulation in nephrin expression in podocytes and many other factors contribute to the pathogenesis of glomerular proteinuria, and the study of their exact molecular mechanisms are in progress(5).

Compared to proliferative glomerulonephritis IMN is less harmful with regard to the risk of rapid progression towards renal failure. The injury in proliferative forms of GN is more aggressive because of the rapid loss of nephrons, disturbance in haemodynamics, tubulointerstitial fibrosis as a result of ischemia to the remaining nephron segment. At first sight, the disease process in MN does not rapidly disturb haemodynamics and the degree of damage is much les. In fact, severe sustained proteinuria induces tubular epithelial cell injury and interstitial infiltration and fibrosis. The pathogenesis of tubular atrophy remains poorly understood. Transforming growth factor-β (TGF-β), in addition to its pro-fibrotic effects, may contribute to renal disease progression by its potent pro-apoptotic activity on tubular epithelial cells. In contrast, epidermal growth factor is implicated in the recovery from renal injury and the protection from apoptotic cell death (6). When porteinuria is present, endothelin-1 expression can also occur in the tubules, endothelin being one of the most potent vasoconstrictors (7). Tubular atrophy and interstitial fibrosis are closely associated with loss of renal function and this point of view is critical for the terapeutic approach to IMN.

**Clinical course and prognosis**

The natural course of IMN is markedly variable. Its main clinical presentation is proteinuria: either nonnephrotic or nephrotic. Forty to 60% of patients never develop ESRD and almost a half of them may have spontaneous remission. Most of the spontaneous partial or complete remissions appear within the first two to three years of initial diagnosis. Remission is often unstable and relapses are common (8). The remainder have a slowly progressive course to ESRD within 5 to 15 years or die of complication of the nephrotic syndrome. These patients usually manifest decline in renal function within the first two years (1, 3, 9, 10). Despite the better control of hypertension and hyperlipidaemia in the recent years the rate of ESRD in MN did not change significantly (1). Once a decline in GFR is established, the spontaneous recovery of normal renal function is an exception in membranous nephropathy (9). Untreated patients with nephrotic syndrome have 10-year renal survival of about 60 % (2). The risk for recurrence of IMN in transplanted kidney is about 30% after 3 years (11).

The variable course of MN necessitates accurate predictors of renal outcome useful to identify the patients who should be treated soon after diagnosis. Advanced age, male sex, severity of initial proteinuria and sustained massive proteinuria, and especially elevated serum creatinin, are the strongest predictors of progression to ESRD along with tubular atrophy, interstitial fibrosis and glomerulosclerosis on biopsy

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(1, 2, 9). The urinary excretion of IgG and $\alpha_1$-microgobulin was found to be significantly associated with the extent of tubulointerstitial damage and predicted the renal outcome (12). Concomitant tubular proteinuria, persisting hypertension and hyperlipidaemia are additional factors for an unfavourable prognosis of MN (3).

Factors that favour both remission and its durability are persistent low levels of proteinuria and female sex (2, 8)

It is difficult to accurately predict the outcome in those nephrotic patients who have normal renal function at the time of biopsy: will they have a spontaneous remission, or they will progress to ESRD? Models have been developed to predict at an early stage the prognosis of the disease using the change in serum creatinin and proteinuria over the initial six month of observation. This algorithm improves the ability to separate patients with a poor outcome from those with a good prognosis (13).

**Therapeutic approaches**

The treatment of IMN remains controversial and suboptimal because of its variable course and the difficulties to predict its outcome. The lack of controlled data about the long-term effects of treatment is another source of controversy.

The conservative approach is based on the suggestion that those patients who probably would evolve into spontaneous remission have not to be exposed to the risk of immunosuppressive therapy (9). Today this approach is intended mainly for patients at low risk: young women, non-nephrotic range of proteinuria, normal or subnormal serum albumin, normal renal function (2).

General agreement exists concerning the indications for immunosuppressive therapy of patients at high risk for progressive course to ESRD (men over the age of 50 years, sustained heavy proteinuria, increased serum creatinine). A comparative study by Torrez and col. (9) showed that immunosuppressive treatment (oral prednisolone for 6 months with oral chlorambucil for 3½ months) in patients with MN and deteriorating renal function was a better therapeutic regimen than the conservative approach. The probability of renal survival without chronic dialysis was significantly higher among patients who received immunosuppressive therapy (90% after 7 years of follow-up) in comparison with patients on conservative approach (20%).

The most controversial issue concerns the treatment of nephortic patients with normal renal function, because of their unpredictable clinical course. Nowadays, the widely used therapeutic approach consist in the administration of steroids and alkylating agents to those patients before the appearance of renal insufficiency. The rational for the early aggressive treatment is based on the fact that persistent massive proteinuria would induce progressive tululointerstitial damage, even in those patients with normal renal function maintained over several years. When intersitital fibrosis appears it would render this therapy ineffective. Moreover, remission would prevent the complications of nephrotic syndrome: infections, cardio-vascular risk and thrombotic events (2). In a randomised controlled study of Ponticelli and col. the probability of survival without developing ESRD at 10 years was 92% in patients given methylprednisolone and chlorambucil versus 60% in controls (14).

**Immunosuppressive treatment**

The standard regiment comprises corticosteroids and alkylating agents. Controlled studies with corticosteroids alone have not shown any benefit (15). The results with steroids and cyclophosphamide for 1 to 3 years have been equivocal and side effects more frequent (2). Some autors administer steroids for 6 months and chlorambucil for 3 months concomitantly (9). The Italian protocol of Ponticelli and col., consisting of 3 methylprednisolone pulses of 1 g each followed by oral methylprednisolone 0.4 mg/kg/day alternating monthly with cytotoxic therapy (chlorambucil 0.2 mg/kg/day or cyclophosphamide 2 mg/kg/day) for three cycles has shown the best evidence of long-term induction of remission and preservation of renal function (14, 15). Prophylaxis with trimethoprim-sulfamethoxazole 3 times weekly during the immunosuppression is recommended by some autors (9). In patients with renal insufficiency as well as in elderly patients side effects are frequent and severe. Methylprednisolon pulses should not exceed 0.5 g/day and the dose of chlorambucil should be 0.1 mg/kg/day (15).

**Alternative therapies**

Cyclosporin A (CsA) alone or combined with corticosteroids has been used for 6 to 12 months in IMN patients with nephrotic-range proteinuria resistant to conventional treatment. Studies suggest that CyA is effective in these cases. Although a high relapse rate does occur, 20 to 39% of the treated patients remain in remission and are non-nephrotic for at least one-year post-treatment, with no adverse effect on filtration function (16, 17).

Mycophenolate mofetil has been effective in MN with the following indications: dependency, resistance or intolerance to steroids, cytotoxic drugs and/or CyA; progressive renal insufficiency; MN associated with diabetes. A significant improvement in proteinuria, serum albumin and cholesterol has been observed with stable renal function (17, 18, 19). The indications for MMF in IMN should be extended and large-scale randomised controlled studies should be carried out.

**Nonimmunosuppressive treatment of MN**

The long-term prognosis of MN depends on the complex approach: reduction of proteinuria, control of blood pressure and treatment of hyperlipidaemia with statins. Blockade of the angiotensin system is the major therapeutic strategy to reduce proteinuria. In addition to their haemodynamic, antiproliferative and antifibrotic effect either ACE inhibitors or angiotensin II type 1 (AT1) receptor antagonists reduce tubular cell apoptosis via suppression of TGF-β gene expression (6). Recent studies show that combined treatment with ACE inhibitors and AT1 receptor blockers has a more potent renoprotective effect compared to monotherapy (20). Combining l-arginine with ACE inhibitors would be a novel renoprotective strategy restoring the nitric oxide/endothelin-1 balance (21).

**New approaches and perspectives**

Recent progress in revealing the molecular pathways of inflammation and immune response should offer alternatives and supplements to the conventional treatment of membranous nephropathy: vaccines, inhibitors of tissue plasminogen activator, humanized monoclonal antibodies, pentoxifyllin, and others.

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