Membranous nephropathy (MN) is the most common cause of adult nephrotic syndrome and it accounts for about 25% of renal biopsies done for this syndrome. Most of the cases are primary or idiopathic in nature while only about one third of the cases are secondary to some known disease. This review describes the recent advances regarding pathogenesis. Membranous nephropathy is an organ specific autoimmune disease. Experimental studies in late 1950s using rat models (Heymann Nephritis) has provided much understanding of pathogenesis of the disease. Role of in situ formation of immune complexes and involvement of complement system was established. Recently the M-type phospholipase A2 receptor (PLA2R) has been identified as target antigen in humans. High titre anti–bovine serum albumin antibodies have been found in children with this disease. It is hoped that in near future non invasive diagnosis and individualised therapy may become a reality.
Experimental studies in late 1950s using rat models has provided much understanding of pathogenesis of the disease. In this model known as Heymann nephritis (HN) a crude preparation of tubular brush-border extract (Fx1I±) is injected into allogeneic animals and this produces proteinuria and subepithelial deposits identical to those seen in human disease. Antigenic target in Heymann nephritis has been identified as a large membrane glycoprotein, gp330, also known as Megalin. It is a member of the low-density lipoprotein receptor family and is found in the clathrin coated pits on the bases of podocyte foot processes.

Further it was shown that immune complexes were formed in situ by using in vitro and ex vivo perfused rat kidneys in a single-pass system. It showed that the antibodies bind in situ to a target antigen intrinsic to the glomerular capillary wall.

Another important finding was that for the development of proteinuria activation of complement was required. After the deposition of immune complexes complement system is activated and leads to insertion of membrane attack complex into podocyte plasma membrane. This produces hypertrophy of podocytes and number of cytopathological changes. These changes permit the passage of proteins through the filtration barrier.

But the findings suggested by HN models have certain limitations when applied to humans. First major limiting fact is that megalin is not expressed on human podocytes. Second despite extensive investigations, a target antigen has been elusive in humans. Third, the pathogenic antibodies in HN are not able to activate the Complement system, whereas the predominant antibody in human membranous nephritis IgG4 is incapable of activating complement system.

The first evidence that established the principle of in situ immune complex formation in humans was established by Debiec et al. They described a case of biopsy proven neonatal MN in an infant born with the nephrotic syndrome. It was found that the mother was genetically deficient in neutral endopeptidase (NEP), and was sensitised during a previous miscarried pregnancy from an NEP-positive father. In her subsequent term pregnancy, circulating anti-NEP antibodies crossed the placenta as well as the foetal GBM, and bounded to NEP in foetal podocytes. Subsequent pathogenic mechanisms were similar to experimental HN model. It was seen that the disease resolved in the infant once the maternal anti-NEP antibody was cleared from its system. In subsequent case series it was seen that proteinuria occurred only in the children of mothers who had both IgG1 and IgG4 anti-NEP. A mother who had only the IgG4 subclass of anti-NEP did not give birth to an affected infant.

Identification of PLA2R as Target Antigen

To identify the target antigen in patients with idiopathic membranous nephropathy, Beck et al used circulating antibodies from adults with MN to detect normal glomerular proteins by using Western blotting. Subsequent analysis with the use of mass spectrometry and confirmation with the use of protein-specific reagents identified a 185-kD glycoprotein in nonreduced glomerular extract, the M-type phospholipase A2 receptor (PLA2R). It was also shown that reactive serum specimens recognised recombinant PLA2R and bound the same 185-kD glycerol extract protein as did the monospecific anti-PLA2R antibody. Anti-PLA2R autoantibodies in serum samples from patients with membranous nephropathy were mainly IgG4, the predominant immunoglobulin subclass in glomerular deposits. PLA2R is a member of the mannose receptor family of proteins. It undergoes constitutive endocytic recycling at the plasma membrane which provide a constant source of PLA2R at the podocyte foot process. Exact role of this protein in the kidney is unknown.

Current sensitivity and specificity analyses show that anti-PLA2R auto antibodies are present in greater than 75% of individuals with Idiopathic MN. Other renal diseases and secondary forms of membranous nephropathy (such as lupus membranous nephropathy) did not involve such auto antibodies.

An association between the clinical features of the disease (proteinuria and the nephrotic syndrome) and the presence and titer of the circulating autoantibodies have been established. In patients who undergo complete remission antibodies disappears while recurrence of antibodies indicate relapse. But this linear relationship is not fully applicable at subnephrotic range proteinuria.

These findings represent a major breakthrough that is likely to have a future role in diagnosis and monitoring of disease activity in idiopathic nephrotic syndrome. At present diagnosis of MN can be made on renal biopsy only. But with detection of these antibodies the diagnosis of IMN may be made without requiring an invasive kidney biopsy. Also, if a biopsy reveals MN, an absence of anti-PLA2R will prompt a more thorough search for secondary causes.

Treatment of MN involves immunosuppressive drugs with many side effects. Assessing the presence of antibodies will help to differentiate between proteinuria due to structural changes or due to
ongoing immunological activity and thus will prevent overtreatment.

Milk and Membranous Nephropathy

Membranous nephropathy is an autoimmune disease. It was proposed that antigens that are not intrinsic to the podocyte can also become planted to the epithelial side of the glomerular basement membrane or the podocyte and form a nidus for immune-complex formation.

Epidemiologic surveys have also identified nutritional elements as risk factors for the development of autoimmunity in genetically susceptible persons.\textsuperscript{25–27} Previous studies showed that exposure to cationic bovine serum albumin could result in membranous nephropathy.\textsuperscript{28} Bovine serum albumin in the cow’s milk can escape from the intestinal barrier and can induce formation of anti–bovine serum albumin antibodies. These days many food ingredients are processed in number of ways that may induce modification of their proteins, which could affect the digestion of these proteins and allow their passage into the bloodstream.\textsuperscript{29,30}

Debiec et al reported a mechanism for childhood membranous nephropathy involving anti–bovine serum albumin antibodies and a modified food-derived antigen, cationic bovine serum albumin, which becomes planted in the anionic glomerular capillary wall and induce in situ formation of immune complexes. In the current study by Debiec et al,\textsuperscript{31} 11 patients with membranous nephropathy had high titre anti–bovine serum albumin antibodies that reacted to a region of bovine serum albumin and had no cross-reactivity to podocyte proteins.

This study has important implications and in childhood MN this should be considered as one of the causes. Eliminating bovine serum albumin or other food products may be helpful in these patients. This may help limit unnecessary immunosuppressive therapy.

Genetic Studies

Recent genome wide association studies in membranous nephropathy linked single-nucleotide polymorphisms in the HLA-DQA1 allele on chromosome 6p21 to PLA2R.\textsuperscript{32}

Recent advances in pathogenesis have thus indicated the interaction of genetic susceptibility and environmental factors in development of membranous nephropathy. So the approach to treatment might change in future to include these factors into consideration and also individualised treatment may become a reality.

References

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