

Trend of Changing Morphological Pattern of Adult Nephrotic Syndrome, Global and Bangladesh Perspective

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Abstract

Nephrotic Syndrome (NS) is a clinical condition characterized by massive proteinuria, hypoalbuminemia, hypercholesterolemia, and generalized oedema. It occurs more commonly in children than in adults, and usually manifests as one of two usually idiopathic diseases: Minimal change NS (MCNS) or focal segmental glomerulosclerosis (FSGS). It has also an incidence of three new cases per 100000 each year in adults. During 70s and 80s membranous nephropathy was considered to be the prime cause of adult NS worldwide. In USA, Brazil, Singapore and South East Asian countries specially in India and Pakistan FSGS has exceeded all other causes of adult NS during last three decades. While in most of the countries of Europe, Australia, Japan, Iran IgA nephropathy has become the main cause of adult NS. Membranoproliferative glomerulonephritis (MPGN) is the predominant cause in certain countries like Russia, South Africa, Singapore etc. In some countries like UAE and Nepal MN is still found to be the main cause of adult NS. In Bangladesh only a few studies are documented which show variable predominant causes of adult NS. It is possibly due to inconsistent renal pathology facilities available in the countries and lack of dedicated renal pathologists.

Introduction

Nephrotic Syndrome (NS) is defined by massive continued losses of urinary proteins, resulting in hypoalbuminemia and oedema. These are associated with complications such as increased susceptibility to infections, thromboembolism, altered lipid and carbohydrate metabolism and losses in binding proteins in the urine¹. It is a clinical condition characterized by massive proteinuria, hypoalbuminemia, hypercholesterolemia and generalized oedema². The NS is defined by a urinary protein level exceeding

3.5 g per 1.73 m² of body-surface area per day. At the turn of the century, clinicians distinguished a nephritic syndrome of inflammatory origin and a NS of presumed degenerative origin. Today these concepts are outmoded, but the term "NS" is clinically useful and has persisted, because heavy proteinuria, irrespective of its origin, is associated with a spectrum of clinically important sequelae, particularly sodium retention, hyperlipoproteinemia, and thromboembolic and infectious complications³.

Nephrotic Syndrome occurs more commonly in children than in adults, and usually manifests as one of two usually idiopathic diseases: Minimal change NS (MCNS) or focal segmental glomerulosclerosis (FSGS)⁴. It has also an incidence of three new cases per 100000 each year in adults⁵. Patients with NS can present to primary and secondary care with diverse symptoms that reflect the primary process or with one of the many systemic complications of the syndrome. Although NS is relatively common in renal practice but there may be delay or overlooked diagnosis as many other conditions like congestive cardiac failure, severe liver disease or allergic reactions may have similar symptoms which are more common in adults⁶.

Glomerular diseases in tropical countries is vastly different in epidemiology, etiology and natural history from those seen in temperate countries; and their prevalence also varies according to socio-economic conditions, race, age and indications for renal biopsy⁷. Over the last few years, studies have shown a changing pattern of these diseases. Previous studies showed that membranous glomerulonephritis (MGN) was the most common cause of adult NS in the United States and Europe while more recent studies have shown that the focal segmental

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glomerulosclerosis (FSGS) is increasing significantly and it has become the most common glomerular disease in African-Americans and Hispanic populations^{8,9}. On the basis of available articles on line this is an attempt to review the causes and morphological spectrums of NS in adult in Bangladesh and surrounding countries.

Pathophysiology of proteinuria in Nephrotic Syndrome- older concept

Passage of plasma proteins larger than 70 kd across the glomerular basement membrane is believed to be normally restricted by a charge-selective barrier and a size-selective barrier. The charge-selective barrier is thought to be due to polyanionic glycosaminoglycans in the glomerular basement membrane, which restrict the passage of small polyanionic plasma proteins (70 to 150 kd), primarily albumin. It is commonly seen in minimal change disease. The size-selective barrier, which is thought to consist of pores in the glomerular basement membrane meshwork, restricts the passage of larger plasma proteins (more than 150 kd). It is commonly seen in membranous glomerulopathy^{10,11}.

Pathophysiology of proteinuria in Nephrotic Syndrome- Newer concept

The mechanisms of proteinuria in primary glomerulopathies are complex and depend on all the components of the glomerular filtration barrier. In primary membranous glomerulopathy, some molecules such as megalin and phospholipase A2 receptor have been considered as being the antigens responsible for subepithelial immune complexes, which change the glomerular permeability¹².

The main primary glomerulopathies that course with proteinuria are podocytopathies. The podocytopathies are characterized by changes in podocytes. These changes may be at the structural or molecular levels, and some proteins have been shown as a pivot of renal injury and proteinuria development¹³. Recent identification of mutations causing glomerular phenotypes, clinical biopsy reports, and experimental model systems reveal a simplified concept of glomerular diseases in which podocyte dysfunction, injury, or loss is a common and determining factor. Toxic, genetic, immune, infectious, oxidant, metabolic, hemodynamic and other mechanisms can all target

the podocyte. Depending on the stage of glomerular development and associated environmental factors, podocyte dysfunction, injury, or loss can result in a broad spectrum of clinical syndromes¹⁴. According to Barisoni et al. podocyte dysfunction may have idiopathic, genetic, or reactive etiologies. The latter involves response to various insults, including mechanical stress, medications, toxins, viral infections, and as yet unidentified circulating proteins. Podocytes react to injurious stimuli in limited manner, which may include: (1) phenotype modification as foot process effacement, with no alteration in podocytes number; (2) apoptosis and loss of podocyte; (3) developmental arrest accompanied by mild proliferative activity; and (4) differentiation and re-entrance into the cell cycle with marked proliferative activity¹⁵. Some changes on the expression of nephrin, podocin, TGF- β , and slit diaphragm components as well as transcription factors and transmembrane proteins have been demonstrated in podocytopathies¹².

Causes of Nephrotic Syndrome

Diabetic nephropathy is the most common cause of nephrotic proteinuria¹⁶. Several primary glomerular diseases account for the great majority of cases of the NS in persons who do not have diabetes. The important primary causes are minimal change disease, membranous glomerulopathy, focal segmental glomerulosclerosis, IgA nephropathy etc. Among the systemic diseases common causes other than diabetes mellitus are SLE (systemic lupus erythematosus), amyloidosis, multiple myeloma, HBV infection etc. The relative frequency of glomerular diseases accounting for the NS varies with age¹⁷.

Minimal Change Disease

Minimal-change disease (MCD) is the most common cause of the NS in children. It accounts for 70 to 90% of the NS in children who are younger than 10 yr and 50% in older children. It is also an important cause of primary NS in adults of all ages, accounting for 10 to 15% of cases¹⁸. Clinically, MCNS is characterized by highly selective proteinuria, i.e. mainly albuminuria, which generally responds well to treatment with corticosteroids. Approximately 90% of children with MCNS and up to 70% of adult patients will respond with a complete remission to a course of corticosteroids¹⁹.

In minimal change disease (MCD) podocytes undergo a phenotypic switch from a cell with foot processes protruding from its basal surface to a cell without basal processes but which has acquired microvillus protrusions on its apical cell surface ('microvillus transformation') similar to those present in renal tubular cells. This remarkable alteration in podocyte structure is not associated with reduction in expression of key podocyte proteins such as nephrin or podocin, such as is seen in forms of focal segmental glomerulosclerosis (FSGS) although podocyte a-dystroglycan, responsible in part for adherence of the podocyte to the underlying GBM (glioblastoma multiforme) is reduced in MCD^{20,21}. Second Northwick Park Heart Study (NPHS2) gene polymorphisms cause proteinuria in patients with minimal change disease (MCD) by depletion of dystroglycan²². It was also reported that a donor kidney from a patient with minimal-change disease functioned normally in the recipient, suggesting that a humoral factor is responsible for the disease²³. Although the identity of the permeability factor has not been confirmed, Th2-derived cytokines— in particular, interleukin-13 (IL-13) and angiopoietin-like 4 – are the current main candidates²⁴.

Focal and segmental glomerulosclerosis

Focal and segmental glomerulosclerosis (FSGS) is a pathological diagnosis highlighting the focal (some but not all glomeruli are affected) and segmental (only a part, not the entire glomerulus, is affected) nature of glomerulosclerosis. The incidence of FSGS appears to be increasing, constituting ~20% and ~40% of NS in children and adults, respectively⁹. Histologically, FSGS is characterized by increased extracellular matrix within the glomerular tuft with obliteration of the glomerular capillary lumen. These sclerotic lesions occur focally and in only some segments of glomeruli, and are typically not associated with immune complex deposition. The location of sclerotic lesions by light microscopy defines the variants of FSGS: perihilar variant (with sclerosis of the vascular pole), cellular variant (associated with hypercellularity of the capillary space), tip variant (involving the part of the glomerulus near the origin of the proximal tubule), and collapsing variant (with one or more glomeruli with global or segmental collapse)²⁶. It is possible that different mechanisms may play a role in the pathogenesis of each variant of FSGS²⁷.

Key in the pathogenesis of FSGS is podocyte damage and loss. Injury to podocytes occurs by four major mechanisms: alteration of the components of the slit diaphragm or interference with its structure, dysregulation of the actin cytoskeleton, alteration of the glomerular basement membrane or its interactions with the podocyte, or alteration of the negative surface charge of the podocyte²⁸.

FSGS involves changes in the slit membrane as well as in the cytoskeleton and cell stress²⁹. It has been proposed that apoptosis, necrosis or loss of cellular adhesive interaction induce podocyte detachment from the GBM, playing a central role in the FSGS-mediated hyperfiltration process. Modifications in the foot process cytoskeleton may lead to NS development, being podocalyxin believed to be responsible for foot process stability³⁰. Mutations in genes coding for key podocyte and slit diaphragm proteins (Nephrin, podocin, CD2-associated protein, FAT, ZO-1, P-cadherin, α -actinin-4 etc) cause hereditary familial FSGS³¹. In collapsing variant, mature podocyte markers including WT1, nephrin, podocalyxin, GLEPP1, the cyclin-inhibitors p21, and p27 and foot processes are lost. In contrast, markers of immature dividing podocytes are acquired and the podocyte becomes capable of proliferating³².

Membranous glomerulopathy

Membranous nephropathy (MN) is one of the most common causes of NS in adults, constituting up to one-third of biopsy diagnoses in some countries⁸. In the majority of cases, the etiologic agent is unknown, and the disorder is termed idiopathic. Secondary MN forms may account for up to one third of cases and are associated with autoimmune diseases (SLE), infections (hepatitis B and C), medications (NSAID), and neoplasias (carcinomas)³³.

MN is characterized by the development of immune complexes (containing mainly immunoglobulins and complement members such as C3 and C5b-9) in the subepithelial space leading to podocyte damage, causing increased production of extracellular matrix proteins and rendering the GBM thick³⁴. In idiopathic MN, the glomerular lesions are mainly caused by autoantibodies against a podocyte membrane protein³⁵, the M-type of phospholipase A2 receptor 1. A strong association with the HLA-DQA1 allele has

been found in patients with idiopathic MN. This allele may facilitate an autoimmune response against antigenic targets such as variants³⁶ of PLA2R1. The detection of anti-PLA2R1 autoantibodies can be useful to recognize the presence of MN in patients with NS and help to diagnosis idiopathic MN in those with a renal biopsy-identified lesion of MN³⁵.

IgA Nephropathy

IgA nephropathy is a primary glomerulopathy characterized by deposition of IgA containing immune deposits in the kidney. It causes approximately 25% of cases of idiopathic NS³⁷. The central pathogenic mechanism is the generation of nephritogenic immune complexes, whose antigen is a poorly galactosylated form of IgA1. These complexes deposit in the glomerular mesangium, eliciting a subsequent inflammatory immune response that produces tissue injury and the clinical sequelae of GN³⁸.

Diabetic glomerulopathy

Diabetic nephropathy is the leading cause of end-stage renal disease. The major pathological findings are mesangial expansion, GBM thickening, and glomerulosclerosis³⁹. Pathologic biopsy reports in type I diabetic glomerulosclerosis and type II diabetic glomerulosclerosis directly link reduced glomerular podocyte number to increased proteinuria^{40,41}. The concept of podocyte loss as a driver of the glomerulosclerotic process in diabetes is well documented. The underlying mechanisms are likely to be in part related to oxidant injury of the podocyte combined with glomerular enlargement resulting from insulin and other growth factors¹⁴.

Changing etiologies of Nephrotic Syndrome

In recent years, attention has been drawn to geographical differences in the epidemiology, aetiology and glomerular pathology of the NS⁴². The pattern of glomerular diseases are different in different countries and changing with time with in the same country probably due to better infection control, changes in environmental pollution, increased awareness of the disease and changes in life expectancy⁴³. In adults, membranous nephropathy (MN) traditionally has been considered the most common cause of nephrotic syndrome (NS). During the last three decades of the 20th century, a significant development in the field of glomerular diseases was an increased frequency of

focal segmental glomerulosclerosis (FSGS) among patients presenting with proteinuria and a primary glomerular disease⁴⁴. According to Haas M et al during the 1976 to 1979 period, the relative frequencies of membranous (36%) and minimal-change (23%) nephropathies and of FSGS (15%) as causes of unexplained NS. In contrast, from 1995 to 1997, FSGS was the most common cause of this syndrome, accounting for 35% of cases compared with 33% for membranous nephropathy⁸. While Braden GL et al shows the increasing incidence of FSGS only in the black (22.6%) and Hispanic (24.6%) populations and not in white individuals in USA⁴⁵. However Swaminathan S et al shows increasing incidence of FSGS among unselected patients from the community of Olmsted County. The majority of the population resided in Rochester the urban center of an otherwise rural area that has an overwhelmingly white population of predominantly Northern European extractions⁴⁶. Later on during 2001 to 2011, Kraus et al. report an apparent reversal of the trend of the late 20th century regarding the relative frequencies of FSGS and MN among primary glomerular diseases in a predominantly adult and primarily African-American and Hispanic population in Chicago⁴⁷.

In a large European study ranging from 1976 to 2005, Hanco JB et al show that before 1985 the predominant cause of primary glomerulopathy was MN (37%), followed by IgA nephropathy and MCD. While after 1985 IgA nephropathy became the predominant cause which reached to 43% followed by MN (26%) and MCD (11%). Incidence of FSGS remains between 4-6% throughout the study duration from 1976 to 2005. The study population constitutes mostly Caucasian origin⁴⁸. Another European study carried out at Moscow during 1970 to 1999 composed of 4400 study population shows MPGN (48.9%) as the major cause of primary glomerulopathy followed by MN (13.4%) and FSGS (7.8%)⁴⁹. Okpechi IG et al also found mesangio-capillary (membranoproliferative) glomerulopathy (19%) as the commonest cause of adult idiopathic NS followed by FSGS (15.7%) and MN (14.9%) in a study⁵⁰ among the South African black population. Incidence of IgA nephropathy was found only in 1.7%. While in Australia Briganti EM et al found IgA nephropathy (34.1%) as the main cause of primary nephropathy followed by FSGS (16.9%) and MN (10.9%)⁵¹. A Brazilian study shows FSGS (29.5%) as

the predominant cause of primary glomerulopathy followed by MN (14.8%), MCD (11.5%) and IgA nephropathy⁵² (11.5%) during 1979 to 1999.

Causes of adult NS in Asia

Changing morphological patterns of NS is also observed in most of the Asian studies. A large study in China during 1979 to 2000 revealed MPGN (Membranoproliferative glomerulonephritis) (40.4%) as the predominant cause of NS followed by IgA nephropathy (39.5%) MN (10.5%). While another study in Northeastern region of China during 2005 to 2009 shows MCD (29.9%) as the predominant cause of adult NS followed by IgA nephropathy (28.7%). In both the studies proportion of FSGS was very less (3.6-5.2%)^{53,54}. Another study in 2009 in China revealed IgA nephropathy accounting for >45% cases of primary glomerulopathy⁵⁵. A Korean study during 1973 to 1995 found MCD (26.6%) as the prime pattern followed by IgA nephropathy (22.1%) and MN (11.8%)⁵⁶. A study in Japan during 1999 also revealed IgA nephropathy (26.8%) as the prevalent cause followed by MCD (15.7%) and MN (10.6%)⁵³. While in UAE during 1978 to 1996, MN (20.1%) was the commonest pattern followed by MCD (18.3%) and FSGS (18.3%)⁵⁷. A Singapore based study carried out during 1976 to 2008 shows Mesangioproliferative GN as the predominant cause of primary glomerulopathy in 1st decade and FSGS as the predominant cause in 3rd decade⁵⁸. While a retrospective study carried out in Thailand shows significant difference between patterns of primary glomerulopathies during 1983 to 1992 and 1998 to 2005. Surprisingly during 1983 to 1992, IgM nephropathy was comprising >60% cases of primary glomerulopathy followed by IgA nephropathy (10.1%) and a very insignificant proportion of FSGS (1.4%). In contrast during 1998 to 2005, IgA nephropathy (29.91%) exceeds the proportion of IgM nephropathy (23.45%) while proportion of FSGS (6.21%) also increased⁵⁹. While in Tehran studies carried out during 80s as well as during 1998 to 2001 found MN being the commonest cause of NS followed by IgA nephropathy and MPGN^{60,61}.

Scenario in Southeast Asia

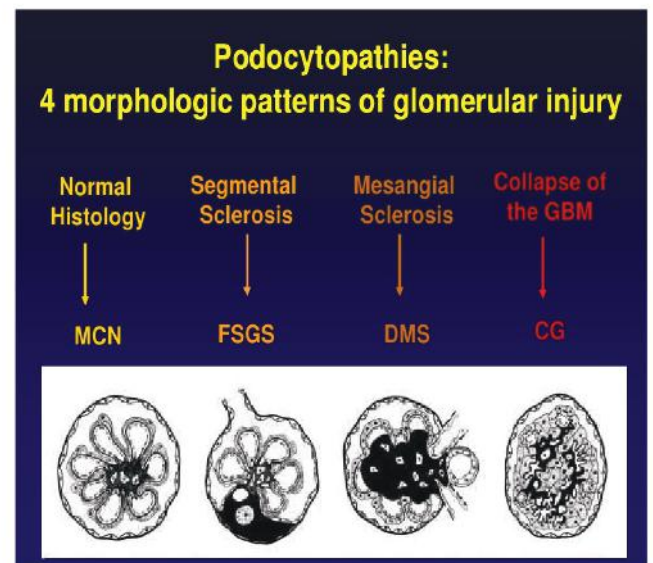
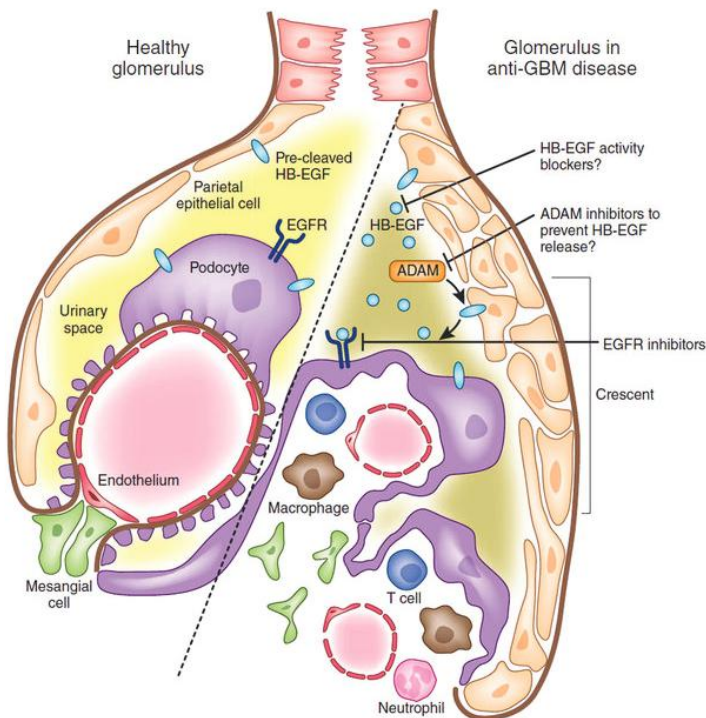
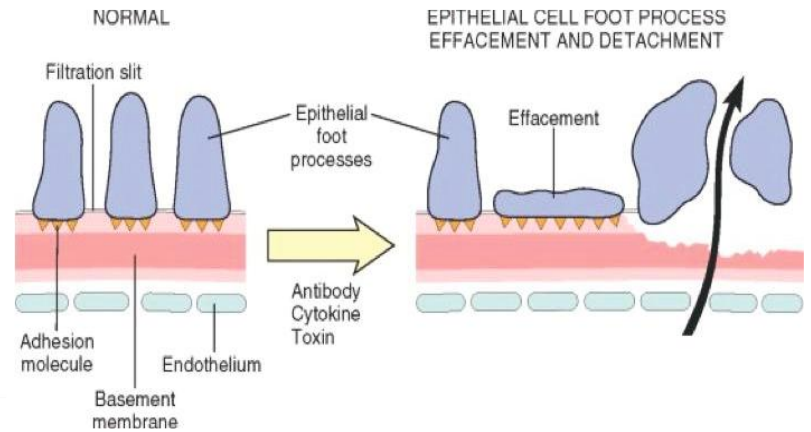
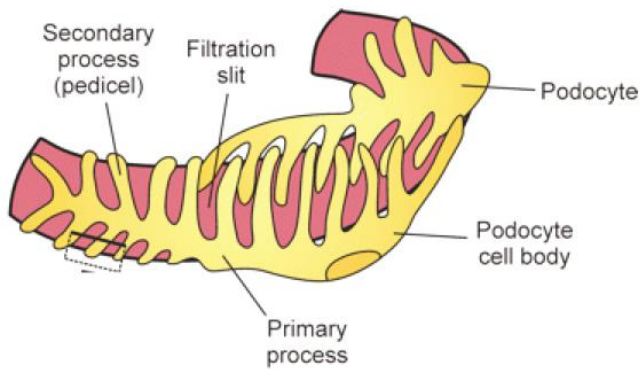
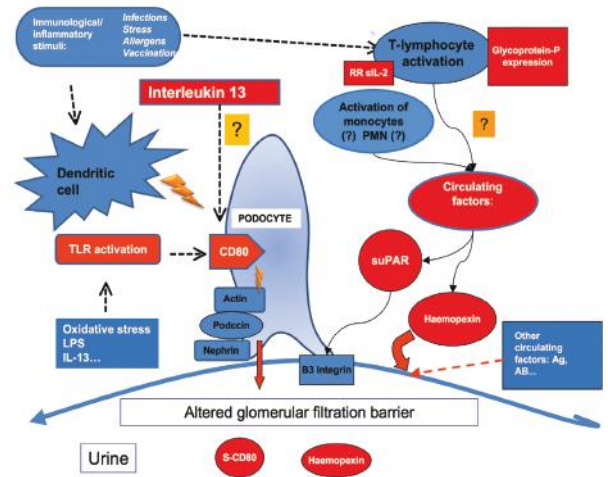
Trend of changing morphologic pattern of adult NS also observed in Indian subcontinent. In PGI Chandigarh during 1964 to 1980 DPGN (Diffuse Proliferative Glomerulonephritis) (36.6%) was the commonest cause of adult NS followed by MCD

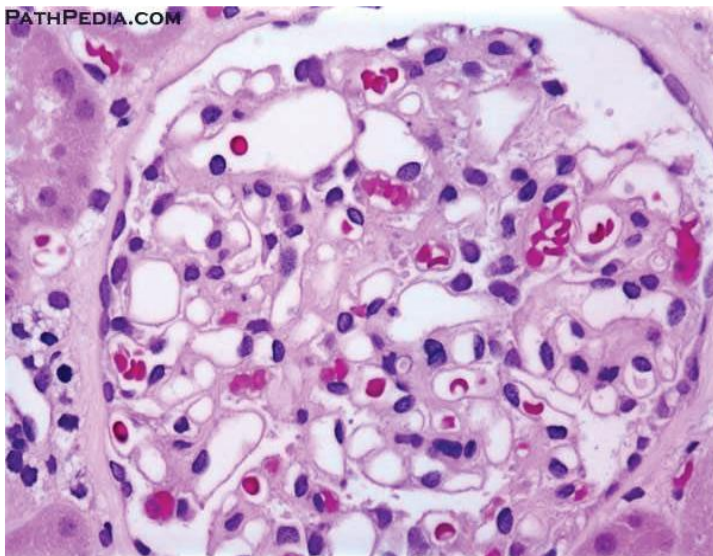
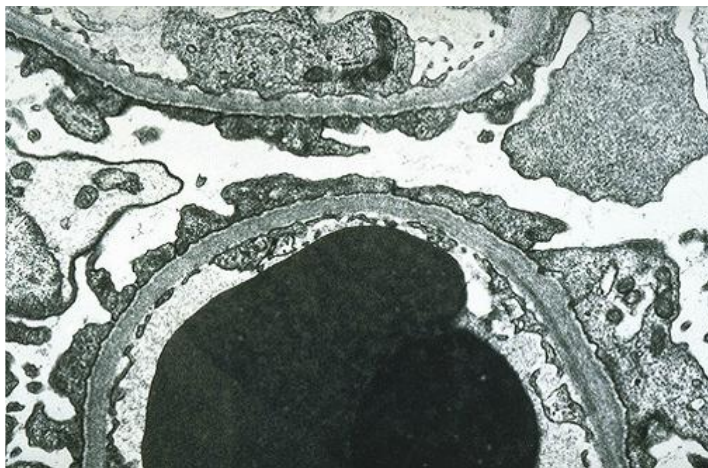
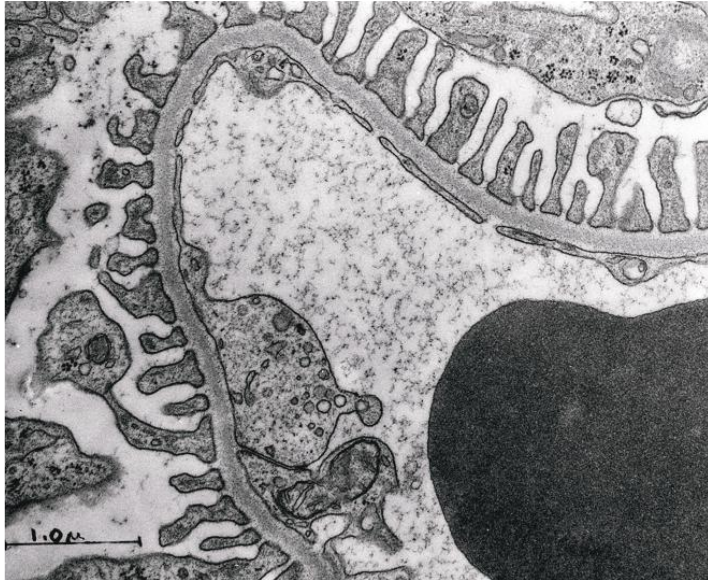
(20.1%) and MPGN (18.6%). During the period there were negligible proportions of FSGS (6.5%). In the same institute another study during 2002 to 2007, there has been a fivefold increase in the frequency of FSGS (30.6%) as a cause of NS along with a three-fold increase in MGN (24.4%) and there has been significant decrease in DPGN (2.8%)⁶². During 1971-85, at CMC Vellore India, Date et al found MCD (35.8%) as the commonest cause of adult NS followed by FSGS (18.6%), MPGN (13.9%) and MN (13.6%). They got only 4.5% IgA nephropathy⁶³. While at the same institute during 1990 to 2001 Balakrishnan et al got FSGS (16.8%) as the predominant cause of adult NS followed by MCD and MN⁶⁴. While during 1990 to 2008 at Hyderabad, Das U et al found MCD (21.8%) as the predominant cause of adult NS followed by FSGS (15.2%) and IgA nephropathy (13.8%)⁶⁵. Reshi et al⁶⁶ also got MCD as the commonest cause of NS at Kashmir during 1987 to 2000. A recent study at Kolkata, Golay et al also found FSGS (27.4%) as the main cause of adult NS followed by MCD (27.1%) and MN (24.6%)⁶⁷. In Pakistan during 1998 to 2005, a Peshwar based study shows MCD as the predominant cause of NS (40%) in elderly patient followed by MN (20.9%) with lesser proportion of FSGS (6.5%)⁶⁸. While during 2007-2008, Abbas K et al found FSGS (28%) as the main cause of NS at SIUT Karachi, followed by MCD (19.5%) and MN (18.5%)⁶⁹. Afterwards Sabir S et al at a naval hospital at Karachi and Mubarak et al at SIUT, also got similar findings with FSGS (>20%) the predominant cause followed by MN (16%) with around 5% of MCD^{70,71}. In Sri Lanka during 1984 De Mel WCP et al reported MN (19.4%) as the largest group followed by membranoproliferative glomerulonephritis (16.1%) among the patients of NS⁷². In Nepal Aryal G et al⁷³ also got MN (42.3%) as the leading cause of NS followed by MPGN (21.9%) during 2001-2007.

Causes of Nephrotic Syndrome in Bangladesh

After detail search only a few published articles on adult NS from Bangladesh were found online. During 2003-2005 at Rajshahi Medical College Tarik MH et al carried out a study on adult NS patients and found mesangioproliferative glomerulonephritis as the commonest (40%) morphological pattern followed by MCD (24.44%) and membranous glomerulopathy (17.77%). Prevalence of FSGS (3.34%) and IgA nephropathy (1.12%) were scanty

in their study⁷². At the same medical college during 2008-2009 Habib MA and Badruddoza SM also got focal and segmental mesangioproliferative glomerulonephritis (29.47%) as the most common histological pattern followed by FSGS (11.58%) and MCD (10.53%). In their study, incidence of IgA nephropathy was 6.85%⁷³. While in Dhaka Medical College a study during 2011 found MN (22.12%) as the commonest cause of NS followed by membranoproliferative glomerulonephritis (11.5%) and IgA nephropathy (11.5%). In their study FSGS was 7.96%⁷⁴. However Ahmed N et al at Dhaka Mitford Hospital got membranoproliferative glomerulonephritis (40.90%) as the commonest glomerulopathy followed by FSGS (22.72%) and MCD (18.18%) during 2009. As per their study MN was only 9.09% and IgA nephropathy was 4.54%⁷⁵.





Conclusion

During 70s and 80s membranous nephropathy was considered to be the prime cause of adult NS. In USA, Brazil, Singapore and South East Asian countries specially in India and Pakistan FSGS has exceeded all other causes of adult NS during last three decades. While in most of the countries of Europe, Australia, Japan, Iran IgA nephropathy has become the main cause of adult NS. MPGN is the predominant cause in certain countries like Russia, South Africa, Singapore etc. In some countries like UAE and Nepal MN is still found to be the main cause of adult NS. In Bangladesh only a few studies are documented which show variable predominant causes of adult NS. It is possibly due to inconsistent renal pathology facilities available in the countries and lack of dedicated renal pathologists.

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