REVIEW

OF

LITERATURE
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Munk (1913) coined the term 'Lipoid nephrosis' to describe the condition in patients who had nephrotic syndrome clinically, but whose disease he considered to be a degenerative process of tubules, not involving glomeruli. The term now refers to uncomplicated primary nephrotic syndrome with no glomerular change by light microscopy. Association between mesengial proliferation and nephrotic syndrome was first suggested by Drummond et al (1966), but was not recognized until reported by Churg et al (1970). Importance of focal glomerulosclerosis in relation to corticosteroid resistance and progression to end stage renal disease was described by Churg et al (1970), in a report for International Society for Kidney diseases in children, 1970.

EXTENT OF THE PROBLEM

Nephrotic syndrome is the most frequently encountered disease among all nephrologic entities.

Nephrotic syndrome develops in approximately 1 in 50,000 children under 16 years as reported by Schlesinger and Rothernberg (1968).

Verneir (1987) reported incidence of Idiopathic nephrotic syndrome with an increased preponderance in males. Literature from west as well as India reveals similar figures (Phadke and Bhave et al, 1990).
Cameroon reported that primary disease accounts for over 95% of cases of nephrotic syndrome diagnosed in children over 1 year of age and 80% of cases in adults.

Minimal change nephrotic syndrome is the commonest type encountered in pediatric practice. It's incidence is known to vary in different populations being 2-3/1 lac children aged less than 15 years per year in Europe and north America (Srivastava et al, 1975), but 11/1 lac per year in Arab children in Libya (Lilenfield, 1980).

Study from Indian subcontinent confirmed Birmingham's statistics, that as in western countries, more than 70% of children presenting with nephrotic syndrome will eventually prove to be having MCNS. It has also been reported that minimal change disease is a more common cause of nephrotic syndrome in Asians than black children in a South African community.

Habib et al (1973) and ISKDC reported that MCNS is the most common pathological entity underlying nephrotic syndrome in Pediatric population.

Incidence of MCNS among Asians is 9.4/1 lac per year and among non Asians, 1.3/1 lac/year. No subpopulation of Asians defined by language religion, or birth place seemed to be a special risk of developing nephrotic syndrome (Feehally and Kendall, 1985).

**GENETIC PREDISPOSITION**

Habib et al (1968) reported familial tendency to acquire nephrotic syndrome in 2-8% of cases.
Affected sibs were found in 3-5% of nephrotic syndrome patients (Moncrieff, 1973).

Habib et al (1973) reported that 3.3% of their patients had affected sibs.

McLean, Makker, Michael et al (1974) reported incidence 1000 times greater, the incidence of nephrotic syndrome in siblings. Histological lesions were also same in them.

Familial occurrence of idiopathic nephrotic syndrome was observed in 3.3% of cases and increased frequency of HLA/B-12 and HLA-A₁/B-8 has been described in several series of patients with MCNS as reported by Robin et al (1981).

Elzonski (1984) reported that 2.7% children in Arabs had affected sibs.

Male : female ratio was described as 2 : 1.

Heymann et al (1972) reported this incidence to be almost 1 : 1.

White (1973) also speculated inherited predisposition as a causative factor for the disease. An European survey which excluded cases of congenital nephrotic syndrome found that 63 to 1877 : nephrotic : children had affected family members.

Clara C Lagneruela (1990) provided additional evidence for an inherited basis for development of steroid sensitive nephrotic syndrome and suggested that this may involve an abnormality of immune system mediated by the major histocompatibility complex.
Whether there is a distinctive polygenic and/or environmental etiology for the development of tendency for familial nephrotic syndrome has not yet been elucidated.

ETIOLOGY

Etiology of commonest variety of nephrotic syndrome MCNS remains an enigma.

Though the definition of nephrotic syndrome remains unchanged - massive proteinuria, hypoalbuminemia and oedema but precise histologic classification of glomerular diseases associated with nephrotic syndrome had drastically improved over the past 10-15 years. The nephrotic syndrome is now a mere clinical manifestation of a large number of morphologically distinct glomerular disorders which in approximately 90% of children, result from primary glomerular disease and in 10% are secondary to systemic disease.

CAUSES OF NEPHROTIC SYNDROME IN CHILDREN

1. Primary renal causes (90-95%) (Idiopathic).
   a. Minimal change nephrotic syndrome (MCNS).
   b. Mesangial proliferative disease.
   c. Focal and segmental glomerulosclerosis (FSGS).
   d. Immune complex glomerulonephritis.
      i. Membranoproliferative glomerulonephritis.
      ii. Acute post streptococcal glomerulonephritis.
      iii. Membranous nephropathy.
   e. Congenital nephropathy.
2. **Systemic Causes (5-10%)**

a. Infectious:

- Malaria
- Hepatitis B
- Filariasis
- HTLV-III infection

- Syphilis
- Schistosomiasis
- Infectious mononucleosis.

B. Toxins/Drugs:

- Mercurials
- Gold
- Probenecid
- Penicillamine
- Captopril

- Bismuth
- Trimethadione
- Renographic medium
- Street heroin
- Antivenoms

c. Allergies:

- Bee sting
- Serum sickness
- Food allergy

- Poison oak
- Inhaled pollens

d. Cardiovascular:

- Sickle cell disease
- Renal vein thrombosis
- Passive congestive heart failure.

e. Malignancies:

- Hodgkin's disease
- Carcinomas
- Melanoma.

- Leukemia
- Wilm's tumor
f. Heredofamilial disease:
   Diabetes mellitus
   Lipodystrophy
   Alport's syndrome
   Nail patella syndrome
   Fabery's disease
   Good posture's syndrome

g. Multisystem disorders:
   Amyloidosis
   Henoch Schönlein purpura.
   Sjogren's syndrome
   Rheumatoid arthritis
   Sarcoidosis
   Dermatomyositis

IDIOPATHIC NEPHROTIC SYNDROME

Diagnosis of idiopathic nephrotic syndrome (primary) is arrived at by exclusion of known causes of nephrotic syndrome such as infection, drug exposure, malignancy, multisystemic disease. The idiopathic forms are further classified by renal biopsy. Children need not always be subjected to renal biopsy since careful clinical study can often lead to accurate diagnosis.

Approximate incidence of primary disease is 90-95% in children and 60% in adults. While approximate incidence of systemic disease is 5-10% in children while 40% in adults.

MINIMAL CHANGE NEPHROTIC SYNDROME

'lipoid nephrosis' was the original term coined by Munk which now refers to uncomplicated primary nephrotic syndrome with no glomerular change by light microscopy.
other descriptive titles are nil (nothing to light) disease or microscopy, foot process disease, idiopathic primary nephrotic syndrome. Based unselected renal biopsy studies of children with nephrotic syndrome, MCNS was found to be histologic lesion in 52-78% of cases (White, 1970; Hayslett et al, 1973; and Habib, 1974).

There are no deposits of immunoglobulins or complement in the kidney. Fusion of foot processes seen on electron microscopy was once thought unique to this syndrome but has been reported in many conditions associated with severe proteinuria.

Saxena and Andal et al (1988) reported minimal change lesion in 68.3% of the 66 patients with idiopathic nephrotic syndrome.

Stanely and Robbins, MD, estimated the incidence of MCNS around 65% in children and 15% in adults.

FOCAL GLOMERULOSCLEROSIS

Mesangial Proliferative

These two are additional histologic lesions often discussed with MCNS are mesangial proliferation and focal glomerulosclerosis. Children with these lesions are clinically indistinguishable at presentation from those with MCNS except for a lack of response to usual regimen of prednisolone therapy. These patients comprised additional 9-15% of the total children with nephrotic syndrome (Habib, et al, 1974).
Saxena et al (1988) reported the incidence of focal segmental glomerulosclerosis (FSGS) around 10.6% as focal sclerosis patients have biopsy picture similar to MCNS, it is considered by some as its variant. Stanely Robbins (MD) reported incidence of FSGS to be about 10%.

MEMBRANOPROLIFERATIVE AND MEMBRANOUS GLOMERULONEPHRITIS

Saxena et al (1988) reported incidence of membranoproliferative glomerulonephritis in 13.6% and 7.5% of membranous glomerulonephritis in their study.

Idiopathic nephrotic syndrome has also been classified by Rance et al (1976) as:
1. Minimal change nephrotic syndrome.
2. Focal glomerular sclerosis.
3. Diffuse proliferative glomerulonephritis.
   Type I - Membranoproliferative/mesengio:capillary.
   Type II - Mesential proliferative
      - Mesengial proliferative with crescents.

PATHOGENESIS

Pathogenesis of MCNS largely remains unclear till now even. Nephrotic syndrome is marked by:

a. Massive proteinuria
b. Hypoalbuminemia
c. Oedema (generalized)
d. Hypercholesterolemia
e. Hypercoagulable state.
f. Increased risk of infections
g. Hypovolumia
h. Elevated BUN and serum creatinine
i. Hypocalcemia.
MASSIVE PROTEINURIA

This is the hallmark of nephrotic syndrome, starting of the chain of events leading to picture what is known as nephrotic syndrome.

The syndrome is fundamentally the result of excessive glomerular permeability to plasma proteins and thus heavy proteinuria is its prime characteristics. The biochemical and ultrastructural mechanisms underlying such increased protein leakage vary in the different diseases causing the syndrome.

LOSS OF GLOMERULAR POLYANION

Glomerular basement membrane is principal structure with thick central electron dense layer - Lamina densa and 2 peripheral electron luscent layers - Lamina vara interna and externa which prevents filtration of macromolecules i.e. beyond molecular weight 70,000 and radius 3.6 nm.

Filtration of macromolecules across glomerulus disease with increasing effective molecular radius approaching zero at a radius of approximately 3.5 nm. There is thus size dependent permeability barrier in the glomerulus. GBM is the principal structure responsible for this size discrimination (Farguhar et al, 1982).

In addition to size glomerulus can discriminate among molecules according to their charge, allowing greater penetration of neutral and cationic molecules compared with anionic molecules of the same size (Deen et al, 1982 and
Venketachalam et al, 1978). This charge dependent restriction is important in the virtually complete exclusion of albumin from filtrate, since albumin is an anionic molecule of a PI ± 4.5.

GBM is composed of :-

i. Collagen (type IV).

ii. Laminin

iii. Polyanionic proteoglycans particularly heparan sulphate this account for so called glomerular polyanion responsible for charge dependent glomerular filtration barrier (Farguhar et al, 1982).

iv. Entactin

v. Fibronutin

vi. Anionic sialoglycoprotein - coats the surface of endothelial and visceral epithelial cells So charge selective barrier of polyanionic proteoglycans and sialoglycoproteins facilitate filtration of cationic proteins and restricting anionic molecules (albumin).

Loss of such anionic sites result in charge selectivity and leakage of anionic molecules such as albumin.

Experimentally, infusion of polycationic molecules such as protamine sulphate which neutralizes anionic sites leads to reversal of albuminuria (Vehaskari et al, 1982).

There is now evidence of loss of charge selectivity in lipoid nephrosis (Dean et al, 1982) what brings about the loss of anionic sites is unknown, but the phenomenon seems also be occur in other glomerular disorders such as diabetic


Blan et al (1973) also proposed that loss of fixed negative ions situated in the sialoprotein layers of glomerular capillary loop leads to increased permeability of low molecular weight polyanionic proteins as albumin.

Experimentally alteration of the highly negative charged GBM results in fusion of epithelial foot processes and loss of interpeduncular filtration sites (Andrews et al, 1979; and Seiler et al, 1975).

In contrast in acute and chronic glomerulonephritis there is structural damage to the glomerular basement membrane (Hulme et al, 1968; and Tiggler et al, 1979).

In these conditions large molecular weight proteins may cross the glomerular basement membrane at areas of structural damage, resulting in poorly selective proteinuria such as commonly found in patients with acute and chronic nephrosis as well as with focal glomerulosclerosis. These two independent alterations of GBM may explain the difference in response to therapy by some patients.

In some patients the fixed negative charge of the GBM may be restored with therapy, but continued alteration in the glomerular pore size may allow persistence of proteinuria even though hypoalbuminemia and edema have resolved.
T Cell Dysfunction

Recently interest has turned to the possibility that MCNS may be related to T cell dysfunction in which humoral factors perhaps lymphokines are produced which alter GBM permeability (Shaloub et al., 1974; Sasdelli et al., 1980).

This hypothesis is based on observations of spontaneous remissions occurring during the course of measles or following live measles vaccination (Yuceoglu et al., 1969), alteration in immunoglobulin levels with elevation of IgM and depression of IgG (Giangiacomo et al., 1975). Relapse of disease have been reported in association with seasonal allergies and atopic disease (Thomson et al., 1976).

Ariela Benigni et al. (1990) made an evaluation of possible relation between renal thromboxane (Tx)A\textsubscript{2} synthesis (measured as urinary secretion of T x B\textsubscript{2}). Urinary T x B\textsubscript{2} was significantly higher in MCNS than in healthy controls and reached its maximum at the time of peak proteinuria. Even during remission, urinary excretion of T x B\textsubscript{2} was still significantly higher than in healthy controls. Results suggested that renal T x A\textsubscript{2} could be regarded as one of the possible mediators of the altered glomerular permeability to proteins in MCNS.

b. **MARKED HYPOALBUMINEMIA**

This is one of the major characteristics of nephrotic syndrome with the serum albumin usually measuring 2.5 g\% or less. Massive urinary loss of albumin is
undoubtedly or major factor in the hypoalbuminemia, but decreased synthesis, increased catabolism or extrarenal losses are additional factors which have been incompletely studied to date. Whatever its cause, heavy proteinuria leads to depletion of serum albumin levels below the compensatory synthetic abilities of liver, with consequent hypoalbuminemia and a reversed albumin globulin ratio.

c. **EDEMA**

The generalized edema is, in turn, the consequence of the loss of colloid osmotic pressure of blood and the accumulation of fluid in the interstitial tissues. There is also sodium and water retention, which aggravates edema. This appears to be due to:

1. Compensatory secretion of aldosterone, mediated by hypovolemia enhanced antidiuretic hormone secretion.
2. Stimulation of the synthetic system.
3. Primary renal effect of uncertain nature.

The decreased colloid osmotic pressure leads to net movement of fluid from vascular system into interstitium or into the 'third space' or from arterial compartment of the vascular space into the chambers of heart or into venous circulation, itself leading to reduction in effective arterial blood volume. This leads to retention of salt and water is insufficient to restore and maintain effective arterial blood volume, it continues, and edema develops.
Edema is characteristically soft and pitting.
Most marked in periorbital regions and dependent portions of body. It may be quite massive with pleural effusions and ascites or condition termed anasarca.

**HYPERLIPIDEMIA**

Hyperlipidemia is a striking feature of nephrotic syndrome. It was first described by Epstein (1913) as a feature of nephrotic syndrome. Patients with nephrotic syndrome have multiple abnormalities of lipoprotein metabolism but the cause and exact nature of these abnormalities are uncertain Jorge Joven et al (1990). Genesis of hyperlipidemia in nephrotic syndrome is complex(Bernard,1982).

Lipoproteins are divided in 4 major groups viz.
1. Chylomicrons.
2. Very low density lipoproteins (VLDL) or prebeta lipoproteins.
3. Low density lipoproteins (LDL) or beta lipoproteins.
4. High density lipoproteins (HDL) or alpha lipoproteins.
   - LDL are carrier proteins mainly of cholesterol 90% and some amount of triglycerides 10%.
   - VLDL are mainly the carrier of triglycerides.

There is a close inverse relationship between hyperlipidemia and serum albumin levels. Low serum albumin levels or diminished plasma oncotic pressure stimulates increased synthesis in liver of cholesterol rich LDL and in more severe cases triglycerides rich VLDL. There is also decreased catabolism of these lipids.
The major carrier of plasma cholesterol LDL and major plasma triglyceride carrier VLDL are elevated early in nephrotic syndrome.

Indirect evidences suggest increased hepatic synthesis of LDL is primary cause of hypercholesterolemia.

VLDL shares same synthetic pathway as albumin in the endoplasmic reticulum and golgi apparatus of the hepatocyte.

\[
\text{Lipoprotein lipase} \\
\text{Under normal circumstances, VLDL} \quad \text{---------} \quad \text{LDL}
\]

1. Low albumin concentration and accumulation of free fatty acid

2. A potent stimulator of lipoprotein lipase activity i.e. plasma apoprotein (apo C-III) is in very low concentration owing to its loss in urine.

Thus hypercholesterolemia and hypertriglyceridemia in nephrotic syndrome results not only from excess production but also from defects in catabolism of phospholipids.

Baxter and Goodman et al (19b0) reported that plasma cholesterol becomes elevated as serum albumin concentration drops below 3 g% but triglycerides remain normal until serum albumin is 1 g% or less.

Thus hypercholesterolemia in nephrotic syndrome cannot be explained on one factor, it seems that multiple factors like:

1. Raised LDL.
2. Hypoalbuminemia
3. Decreased lipoprotein lipase activity.
4. Raised alpha and beta globulins in serum are
responsible for its (Bhandari and Mandowara, 1980).

ATHEROSCLEROSIS

Although evidence is strong that increases in total and LDL cholesterol are important in the pathogenesis of atherosclerosis in general population, the extent to which hyperlipidemia contributes to the development and progression of atherosclerosis in patients with nephrotic syndrome is unclear. The duration of exposure to lipid abnormalities induced by the nephrotic syndrome must be taken into account, since atherosclerosis evolves over an extended time. Although incidence of atherosclerotic vascular disease appears to be higher in patients with persistent long standing nephrotic syndrome the presence of hypertension, hypercoagulability and other risk factors for vascular disease makes it difficult to define the role of hyperlipidemia in vascular disease associated with nephrotic syndrome (William et al, 1990).

Dietary measures to reduce serum lipid concentrations are often unsuccessful, whereas newer antilipemic agents may be effective (Vega et al, 1988; and Rabelink et al, 1988).

Simvastatin reduces hyperlipidemia associated with nephrotic syndrome (Davison et al, 1984). It is effective and safe in long term management of nephrotic hyperlipidemia and may induce partial remission in nephrosis (Robelink et al, 1990).
'Lipiduria' follows hyperlipidemia, since not only albumin molecules but also lipoproteins leak across the glomerular capillary wall. Lipid appears in the urine either as free fat or as 'oval fat bodies' representing lipoprotein resorbed by tubular epithelial cells and then shed along with degenerated cells.

**HYPERCOAGULABLE STATE**

Hypercoagulable state is due, in part to loss of anticoagulant factors (antithrombin III) and anti plasmin activity through the leaky glomerular in urine and there are also thrombocytosis and marked increase in serum factors V, VIII and VII and fibrinogen due to increased synthesis or a reduced volume of distribution (Kauffman, 1978; Vaziri, 1984).

Renal vein thrombosis, once thought to be a cause of nephrotic syndrome, is most often a consequence of this hypercoagulable state (Wagoner et al, 1983). In patients with nephrotic syndrome there is increased incidence of renal vein thrombosis (Kendall, 1971; Vaziri, 1983).

More recently, a report of increased platelet aggregation in patients with nephrotic syndrome has again suggested the presence of a hypercoagulable state (Lundin et al, 1980). This report found increased levels of beta thromboglobulin, a platelet specific protein released upon platelet aggregation in patients with nephrotic syndrome.
INCREASED RISK OF INFECTIONS

These patients are particularly vulnerable to infections, especially with staphylococcus and pneumococci. The basis of this vulnerability could be related to loss of immunoglobulins to low molecular weight complement components (Factor B) in urine.

Infections such as septicemia, cellulitis, peritonitis and pneumonitis can occur due to streptococcus pneumonie.

However, an almost equal number of inpatients are caused by gram negative organisms as E.coli, pseudomonas and H. Influenze.

Prophylactic antibiotic therapy is not indicated but close observation for potential infection during the time of edema is essential in children especially who develop fever.

Other reasons proposed for increased susceptibility to infections in patients with nephrotic syndrome are:

c. Abnormal macrophage function because of lipid ingestion.
d. Sluggish circulation because of edema.
e. Suppressed immunity due to steroid therapy (Chicken Pox and rubeola infections).

Earlier pneumococcal infections were commoner but now gram negative organisms predominate (Wilfret et al, 1968 and Speak et al, 1974).
With edema insignificant scratch or abrasion of skin can cause cellulitis.

Peritonitis may result when ascites is present compression of lung by pleural effusion and elevation of diaphragm by ascites increase the susceptibility to pneumonia.

HYPOVOLEMIA

Hypovolemia may cause postural hypotension, acute renal failure or circulatory collapse (Reader et al, 1962).

HYPOCALCEMIA

Patients with nephrotic syndrome often have a falsely low levels of serum calcium because of the hypoaalbuminemia. But the chronic nephrotic syndrome patients may demonstrate symptoms of hypocalcemìa secondary to low ionized serum calcium.

Mechanism of hypocalcemìa is still uncertain but blood levels of 25 hydroxy vitamin D, 1, 25 hydroxy vitamin D and 24, 25 dihydroxy vitamin D have all been reported to be significantly low in patients with nephrotic syndrome owing to loss of vitamin products in urine (Paul et al).

More recently diminished intestinal absorption true hypocalcemìa, low circulating calcidol levels, secondary hyperparathyroidism have been noted. Most alterations noted are transient and normalised on remission.

Children with relapsing protracted nephrotic syndrome are at risk of developing metabolic bone disease.
Clinically, a few children with MCNS with onset between 1-2 years develop rickets (Bernard, 1982).

**PROVOCATIVE FACTORS**

**Allergic Disorders**

Meadow et al (1981) reported positive history of an allergic disorder in 34% children with nephrotic syndrome. Positive history was present in 31% children with relapsing nephrotic syndrome.

Disorders noted were asthma, eczema, recurrent urticaria, hay fever and allergic rhinitis.

In 50% of these children at least one of these allergic disorder was present in first degree relatives of the patient. This was significantly higher incidence of allergic disorder in first degree relatives of control group.

**Seasonal factors**

Meadow et al (1981) reported that onset of nephrotic syndrome was less common in April, May and June. This was the pollen season in this region, whereas house dust mite another common allergen was commoner in Sept. and October. They could not associated this with timing of occurrence of nephrotic syndrome.

**Upper Respiratory Tract Infection**

This was a consistent fact given by the parents that onset of nephrotic syndrome or relapse of nephrotic syndrome was preceded many a times by cold or less often
cough. Relapses occurred usually within 3 days of such upper respiratory tract symptoms.

Fifty percent of relapsing nephrotic syndrome patients had such history two times and 25% of relapsing nephrotic syndrome gave history of upper respiratory tract infection prior to every relapse (Meadow et al, 1981).

HISTOPATHOLOGY

Idiopathic nephrotic syndrome has been classified on histopathological basis as:

a. Minimal change nephrotic syndrome.
b. Focal or segmental glomerular sclerosis.
c. Diffuse proliferative glomerulonephritis.
   i) Membranoproliferative/or mesangiocapillary type I, type II and type III.
   ii) Mesengial proliferative.
   iii) Mesengial proliferative with crescents.
d. Membranous nephropathy.
e. Congenital nephrotic syndrome.

MINIMAL CHANGE NEPHROTIC SYNDROME (MCNS)

Thus entity accounts for around 55% cases of nephrotic syndrome. Nephrotic syndrome is associated with diffuse loss of foot processes of epithelial cells in glomeruli that appear virtually normal by light microscopy (Phadke et al, 1990). Pre-requisite for the diagnosis of MCNS at light microscopy is exclusion of abnormal findings. Electron microscopy reveals fusion of foot processes.
Etiology of MCNS remains an enigma but several features of disease point to immunological basis.

There is loss of negative charge which is associated with:

1. Enhanced filtration of circulating polyanions, mainly albumin due to loss of heparin sulphate, proteoglycan.

2. Change in shape of epithelial cell leading to familial disappearance of foot processes due to reduction of sialoglycoprotein cell coat.

Saxena (1988) studied 45 patients of MCNS with 42% showing no significant morphological alterations while 44.7% showed mild mesangial alterations in the form of mesangial hypercellularity (1+) and mesangial thickening and in 15.1% focal glomerular obsolescence.

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

It accounts for 10-15% of cases of nephrotic syndrome. Churg et al (1970) first brought this entity to light. It was noted that a small proportion of children responded poorly to steroids and in these renal biopsies showed occasional glomeruli exhibiting an area of sclerosis confined to only one segment of glomerulus.

Habib (1973) divided FSGS in two groups:

a. Focal and segmental sclerosis.

b. Focal glomerular obsolescence.

In focal and segmental sclerosis changes are first apparent in juxta medullary glomeruli and are limited to part of stuff. In focal glomerular obsolescence 15%
glomeruli are completely sclerosed and there is interstitial and tubular damage.

The characteristic degeneration and focal disruption of visceral epithelial cell is thought to represent accentuation of the diffuse epithelial cell change typical of lipoid nephrosis. It is thus pronounced epithelial damage that is the hallmark of FSGS.

Saxena (1988) found on light microscopy FSGS in 10.6% of cases. Studies showed in 4 cases minimal glomerular changes of diffuse mesengial hypercellularity and later focal sclerosing lesion on subsequent biopsy. In two cases glomeruli showed global sclerosis with presence of crescents 28.5% and synechie 20% and intense infiltration of interstitium by mononuclear cells. Small areas of hyalinosis in sclerosed segment were found in almost all cases.

Increasing evidence shows that these represent variations of the disease rather than separate entity. Thus several of these changes may be present in the same biopsy. Alternatively a patient showing MCNS in first biopsy may subsequently show FSGS (Waldnerr, 1983).

Whether FSGS represents a distinct disease or is simply a phase in the evolution of a subset of patients with lipoid nephrosis is a matter of debate with most investigators favouring the latter possibility (Goldzer et al, 1984; Rosen et al, 1981).
Presence of even a single segmentally sclerotic glomerulus in a biopsy specimen warrants for diagnosis of FSGS.

FSGS in contrast to MCNS is often resistant to steroid therapy and carries a substantial risk of progression to end stage renal disease. Repeated renal biopsy may point out the progression of initially MCNS diagnosed patient to FSGS or initially biopsy may have missed glomeruli with already existing sclerotic lesions. Alternatively it is considerable that although FSGS was indeed absent at the time of biopsy abnormal pathogenic process had already come into play in this unique subset of MCNS, leading subsequently to development of morphologically identifiable FSGS detected only on re-biopsy.

**DIFFUSE PROLIFERATIVE GLOMERULONEPHRITIS**

Membranoproliferative/Mesangiocapillary glomerulonephritis (MPGN)

This condition was first described in 1965. By light microscopy, it is seen that GBM is thickened often focally, most evident in peripheral capillary loops, glomerular capillary wall shows double contour or tram track appearance evident on PAS stains.

MPGN has two main types (I and II).

Type I MPGN (Two thirds of cases)

It is characterised by subendothelial electron dense deposits. Most cases of type I MPGN present evidence of immune complexes in glomerulus and activation of both
classical and alternate complement pathway.

**Type II MPGN**

Dense deposits are present in lamina densa of GBM(intramembranous). Most patients with type II have abnormalities which suggest primary activation of alternate complement pathway (normal C₁ and C₄ and diminished factors and properdin).

**Type III MPGN**

It is very rare entity. Exhibits both subendothelial and subepithelial deposits, associated with GBM disruption and reduplication.

**Mesengial Proliferative Disease**

Association between mesengial proliferation and nephrotic syndrome was first suggested by Drummond et al (1983). But it was not well recognised until reported by Churg et al, the ISKDC. There is only slight diffuse increase in mesengial cells together with a moderate increase in mesengial fibrils from 2.5 to 5.3% of patients with nephrotic syndrome will have this lesion on renal biopsy (Habib et al and Andrews et al).

**Membranous Glomerulonephritis (MGN)**

Light microscopy reveals diffuse deposits giving the appearance of 'Spikes' on the epithelial side of capillary GBM and absence of cellular proliferation. Children may have this disease but it is common in adult
only. It accounts for less than 5% of cases of idiopathic nephrotic syndrome in children.

MGN occurs in 10% of patients with SLE. It is also associated with certain infections (syphilis, malaria, hepatitis B) mercury, gold penicillamine), and tumors(Lung, carcinoma, melanoma)(Arnaut et al, 1982). In 85% of patients with MGN none of these associated conditions exist and term idiopathic MGN is used in such cases (Noel et al, 1979).

It is supposed to be a form of chronic antigen antibody mediated disease. Circulating immune complexes are found in 15-25% of cases (Couper et al, 1982). Only in small number of cases specific antigens have been identified in the deposition.

CONGENITAL NEPHROTIC SYNDROME

It may appear in first 3 months of life. In both the hereditary (Finnish) and sporadic forms the glomeruli may appear to be normal. Dilatation of the proximal convoluted tubules gives a characteristic 'microcystic' appearance and as disease progresses.

Minimal lesion nephrotic syndrome and focal glomerulosclerosis also can begin in first year of life (Kaplan, 1974).

RENAL BIOPSY IN NEPHROTIC SYNDROME

Renal biopsy is usually not indicated in children with steroid sensitive nephrotic syndrome because about 95% have minimal change lesion with an excellent long term
prognosis (Bernstein, 1981).

ISKDC (1982) recommended that occurrence of frequent relapses is not in itself an indication for either an initial or repeat renal biopsy since 95% of 521 children with nephrotic syndrome had 3 or more relapses in first 6 months after initial response.

In frequently relapsing cases responding to steroid therapy, having developed severe steroid toxicity, growth retardation, cataract, severe cushingoid.

Syndrome or failure of steroids to induce remission form sufficient ground to perform renal biopsy. Diagnosis should be revised to focal glomerulosclerosis or mesangial proliferative disease etc and then patients given a trial of cyclophosphamide.

It was a policy of Bruce and Mcdonell et al (1976) to do biopsies in those nephrotic children who were less than 1 or more than 6 years of age or who failed to respond to an initial 2 weeks course of corticosteroids given in a daily divided doses as they found 60% of ultimately steroid responsive patients who showed resolution of proteinuria with 2 weeks of therapy so only a minority of patients had biopsy.

Renal biopsy is necessary before instituting cytotoxic drug therapy in cases suspected other than MCNS since steroid therapy is ineffective and it may even be harmful (Cameron, 1968).

Biopsy should be performed in any patients who has become steroid resistant and in children with frequently
relapsing disease with serious side effects of steroids. In children aged 9 to 12 months or over 10 years the proportion of cases due to MCNS is smaller but routine biopsy.

Meadow et al (1981) reported that out of 84 steroid responsive children, in 41 renal biopsy showed minimal change. In rest biopsy was not undertaken as they were likely to show histological lesion other than minimal change because their clinical course and findings were even more typical of MCNS than 41 who underwent biopsy.

ISKDC (1981) reported that 25% of all non responders to steroids showed MCNS lesion on biopsy.

In absence of these findings it is reasonable to assume that the disease is minimal lesion and biopsy is not necessary before the start of treatment.

IMMUNOFLUORESCENT STUDIES

Minimal change nephrotic syndrome

Characteristically there are no deposits of immunoglobulins or complement in the kidney excluding classical immune complex mechanisms. Although immune complexes have been found in some patients with MCNS (Lewinsky et al, 1978).

On immunoflorescent study some times non specific axial arteriolar staining particularly with IgM and complement is seen (Paul et al, 1982). Some cases of MCNS have deposition of IgM which is considered insignificant by pathologists. Deposition of IgG or complement components is absent (Phadke and Bhave, 1990).
Carvallo et al (1981) found in patients of MCNS, no changes by light microscopy or immune fluorescence though some times deposits of C₃ and IgM in mesangium were found.

Saxena et al (1988) studied 45 cases of MCNS but IgG, IgM and IgA, C₃ were not seen in any of it, irrespective of their light microscopic appearance.

Mehta and Ali (1985) studied biopsies of 30 patients with nephrotic syndrome by immunoflourescent studies. Eighteen out of 30 cases had MCNS on light microscopy, 10 of these 18, showed no immunoflourescence of kidney tissue. Eight (44%) cases showed coarse to fine granular deposits of IgM (with IgG in 2 and C₃ in one) however, no correlation was found between steroid response and positive immunoflorescence.

Prasad (1977) reported deposits of IgM and occasional mesengial deposits of C₃ in MCNS. In a group of children with IgM deposits, focal segmental IgM deposits were present in approximately 1/3 of both responders and non responders (Mota Hernandez, 1979).

Although it seems certain that some patients with MCNS do have IgM deposits, the clinical and pathological significance of these deposits is yet to be ascertained.

**FOCAL GLOMERULAR SCLEROSIS**

Immunoflourescent studies show deposits of IgG, C₃ and C₄ complement and fibrin(fibrinogen) within the hyline masses in the sclerotic areas, but non sclerotic areas show either no staining or slight staining with IgM and C₃.
Electron microscopic studies showed diffuse thickening of GBM, partial or complete capillary collapse with presence of focal or diffuse mesangial hypercellularity 2+ to 3+, intercapillary foam cells (60%) and electron dense deposits in basement membrane as well as mesangium. In 7 cases of FSGS studied 5 showed deposits of IgM (only 71.4%) while in 2 cases IgM and C₃ (28.5%).

Membranoproliferative glomerulonephritis

Type-1 showed C₃ deposited in granula pattern and IgG and early complement components (C₁q and C₄) are often also present suggesting immune complex pathogenesis. In type II, C₃ is present in irregular granular linear foci in the basement membranes on either side, but no within the dense deposits. C₃ is also present in the mesangium in characteristic circular aggregates (mesengial rings). IgG is often absent and early acting complement components (C₁q and C₄) are usually absent from the deposits.

Membranous Nephropathy

Immunoflourescent microscopy shows fine granular deposits of IgG occasionally of C₃ along the GBM.

All 5 cases studied by Saxena et al (1988) showed fine to coarse deposits of IgG and C₃ along glomerular capillary wall, corresponding to electron dense deposits seen subepithelially with the electron microscope.
IMMUNOLOGICAL CORRELATION

Nephrotic syndrome as an immunologically induced disease was first seriously considered in 1907 when Shick, Bell and Clawson produced glomerulonephritis in laboratory animals by injecting either anti whole kidney, anti-glomerular or antibasement serum or by intravenous injection of foreign proteins. Reduced concentration of gamaglobulins in serum of patients with nephrotic syndrome was reported as early as 1940 (Longstrom, 1940). Cooper (1967) suggested involvement of complement in a variety of disease processes.

Now it is well known that nephrotic syndrome has a profound effect on the concentrations of several serum proteins. Levels of IgG and transferrin are low while those of haptoglobin, alpha-2 macroglobulin and IgM are elevated. Lewis et al (1971), Giangiacoma et al (1975), Michael et al (1873). Fragmentary observations have indicated that this syndrome can also affect the levels of certain complement components.

Because serum levels of individual complement components are helpful in the diagnosis of various glomerulonephritis and in assessing the pathway of complement activation. It is of value to document the effect of a nephrotic syndrome, often present in patients with hypo-complementemic glomerulonephritis, on the complement profile.

The cause of MCNS still remains unclear although several immunologic mechanisms have been postulated.
Shalhoub (1974) stated that exact pathogenesis of minimal change nephrotic syndrome is not known, although several disturbed immunological parameters are found in children.

Some characteristics of disease like association of relapse with seasonal allergies, atopy, low levels of IgG concentration both at the onset and during a relapse suggest that immunological mechanisms do play an important role in its pathogenesis (Thomson et al., 1976).

The clinical association of MCNS with atopy with malignancies such as Hodgkin's disease with known depression of cell mediated immunity, its response to immunosuppressants such as steroid and cyclophosphamide as well as remission induced by measles infection, have given rise to speculations regarding the possibility of immunological abnormalities in the causation of this disease. Depression in cell mediated immunity, abnormalities of immunoglobulin synthesis and the association of this syndrome with specific antigens of the HLA system have been described.

A lymphokine that increases vascular permeability (vascular permeability factor) has also been identified in the sera of patients with active disease (Tyrone Mehin et al., 1984).

Decreased delayed hypersensitivity skin responses to PPD have also been reported. Fodor-Petal (1982), Hoyer et al (1982) stated that hypoalbuminemia, hyperlipidemia and zinc deficiency that accompany this disease are known to have depressive effects on cell mediated immunity.
Giangiocoma (1975) observed decreased levels of IgG have been observed in idiopathic nephrotic syndrome irrespective of the course of nephrotic syndrome.

**EFFECT OF HUMORAL IMMUNITY**

Now it is well known that nephrotic syndrome has a profound effect on the concentration of several serum proteins. Levels of IgG and transferrin the low while those of haptoglobins alpha$_2$ macroglobulin and IgM are elevated.

Studies on the levels of serum immunoglobulins showed significantly lowering of serum IgG associated with proportionate rise in the levels of serum IgM at onset (Giangiocoma et al, 1975; and Glassock et al, 1986; and Sober et al, 1976).

Giangiocoma et al (1975) reported decreased levels of IgG in patients with idiopathic nephrotic syndrome irrespective its course.

Andal et al (1989) reported very low levels of IgG at onset in frequently relapsing children with MCNS, which persisted during remission.

Other reported no significant difference in immunoglobulin levels estimated at onset and at relapse.

Loss of IgG contributed to the reduced serum levels to some extent. However, lowered levels in non proteinuric patients during remission suggested that there is some additional factor accounting for the lowered levels of IgG even after long term remission.
The concentration bears linear correlation.

Groshang et al (1973) noted raised serum IgE in patients with MCNS.

No change in immunoglobulin levels was observed between frequent and infrequent relapsers by Glassock et al (1986).

Selectively decreased titres of serum IgG and IgA with increased or normal titres of IgM have been observed in MCNS by Hoyer (1982) and Tyrone Melvin et al (1984).

Mehta and Ali (1985) studied humoral immunity in a group of 18 patients by measuring IgG, IgM and IgA levels. IgG levels in children with active MCNS was very low. The IgM and IgA levels were within normal limits.

This depression in IgG cannot be explained on urinary losses alone. Increased catabolism may play a part. It has been postulated that the T cell mediated conversion from IgM to IgG synthesis may be defective (Merlan et al, 1982).

Recently decreased in vitro IgG synthesis has been demonstrated in the lymphocytes of patients with MCNS. Elevated serum IgE levels have been documented in some patients with MCNS (Schulte-Wissermann et al, 1979).

Higher incidence of atopy in children with MCNS and their first degree relatives as compared to controls was reported by Meadow (1981).
The mean levels of IgM were 303.1±112.4 mg%, 164.0±50.4 mg% and 252.4±76.2 mg% at onset, remission and relapse respectively (Andal, 1989) while mean value of control was 169±89.1 mg%. Sudhir and Yuceoglu (1985) reported the IgM levels to be 65±25 mg% in patients with MCNS type while in controls it was 58±23 mg%.

Yokoyama (1985) reported the mean IgM levels as 267±28, 263±39, 269±41, 234±25, 186±21 and 126±13 mg% in nephrotic syndromes, initial episode, relapse, unstable remission, stable remission and in controls respectively and levels of IgG were reported by Andal et al (1989) as 370.3±201.2, 714±2374.2, 527.2±299.1 mg% at onset, remission and relapse respectively while it was reported in controls as 1229.2±292.7 mg%.

Gupta et al (1985) reported IgG levels to be 762±209 in nephrotic syndrome with MCNS type while in controls it was 923±256 mg%. Serum IgG was significantly decreased in 7 of 11 patients.

Mehta and Ali (1985) reported serum IgG levels in MCNS group as 576±164.1 mg% while in controls it was 1072±348 mg%.

Yokoyama et al (1985) reported IgG levels as 642±88, 521±110, 891±78, 1051±73 and 1464±86 mg% in initial episode, during relapse, in unstable remission and in stable remission respectively while it was 1276±54 in controls.
EFFECT OF CELL MEDIATED IMMUNITY

The concomitant elevation of IgM with lowering of IgG, may be related to the fact that nephrotic syndrome is primarily a thymic cell dependent immune defect. Cells which normally produce IgM class of antibody before converting to the synthesis of IgG and IgA fail to elicit this response resulting in elevated levels of IgM (Davie et al, 1974 and Eisen, 1973).

Further evidence to support T cell dysfunction comes from studies in which extracts from cultured lymphocytes in 50% of patients with MCNS (Sasadelli et al, 1980), caused enhanced vascular permeability when injected subcutaneously in guinea pigs (Lagru et al, 1975).

Recently interest has turned to the possibility that MCNS may be related to T cell dysfunction in which humoral factors, perhaps lymphokines are produced which alter glomerular basement membrane permeability (Sasadelli et al, 1980).

This hypothesis is based on observations of spontaneous remissions occurring during the course of measles, or following live measles vaccination (Tuceoglu, 1989), alteration in immunoglobulin levels with elevation of IgM and depression of IgG and the frequent occurrence of nephrotic syndrome in patients with Hodgkin's disease (Long and Hall et al, 1977).

Other immunologic aberrations have also been described such as lymphotoxicity to cell cultured renal
epithelial cells by lymphocytes obtained from patients with MCNS and inhibition of normal blastogenesis by serum from patients with active MCNS (Itika et al, 1979).

MCNS is a disease of unknown etiology. Shalhoub (1979) suggested that MCNS be related to a T cells disorder particularly a disorder of suppressor T cells. Since then a number of studies have suggested multiple immunologic abnormalities in MCNS. Cellular and molecular basis of these defects are not known. Several investigators have reported evidence of a pathogenic role of T cell mediated immunity. Moorolhy et al (1976), Iitaka and West (1979), Minchin (1980) have reported presence of serum inhibitory factor during active stage of disease but lacking during remission.

Studies on T cell subpopulation in children with MCNS have shown not only decreased levels of T helper and suppressor cells but also functional impairment of T helper cells (Sasadelli et al, 1980).

Impaired T cell activity may contribute to the failure of B cells to switch from IgM, synthesis to IgG. Andal et al (1989) showed the functional impairment of T helper cells to persist during remission though quantitative estimation showed a significant rise from the levels at onset.

Taube et al (1981) reported significant lowering of suppressor cell function in children following long
term remission with cyclophosphamide. They observed greater suppressor cell activity in children who continue to relapse even after cyclophosphamide therapy.

Yokoyama (1985) reported that immunological abnormalities in MCNS are characterised by acceleration of the IgE and IgM producing system and impaired maturation of the IgG producing system and impaired maturation of the IgG producing system despite normal differentiation from IgM producing IgG producing system, possibly caused by T cell dysfunction.

Mehta and Ali (1985) assessed cell mediated immunity by absolute T cell count, the blastogenesis index and the skin reactivity to dinitrochlorobenzene (DNCB). There was a significant depression in all 3 parameters.

Steroid administration tended to correct abnormalities of not only T lymphocyte subsets but also of beta lymphocyte subsets and serum IgG levels. Hereby causing improvement of clinical symptoms.

Disorders of beta lymphocyte function and IgG producing mechanisms who are controlled by T lymphocytes may be involved in the etiology of MCNS and steroid might correct these disorders (Yokoyama et al, 1985).

Chen (1987) reported enhanced suppressor cell activity resulting in increased IgM and reduced IgG production in MCNS children.
EFFECT ON COMPLEMENT SYSTEM

Lange (1960) demonstrated lowering of plasma complement activity after an attack of nephritis. Persistent hypocomplementaemia was observed in cases with membranoproliferative cases. Plasma complement activity was estimated by one of its components C₃ (Klemperer et al. 1965). The involvement of complement in a variety of disease processes had been suggested by Cooper (1967).

The measurement of serum levels of specific components of the complement system is helpful in the diagnosis of several forms of chronic glomerulonephritis and in evaluation of therapy.

Prasad et al. (1980) studied plasma C₃ complement levels and found hypocomplementemia in 32% of cases initially but on follow up persistently low levels were observed only in 8% and among these 6% had membranoproliferative glomerulonephritis and belonged to low selectivity group. Only one case out of 4 with persistent hypocomplementaemia had high selectivity. Five out of 16 cases with high selectivity were hypocomplementemic.

Since nephrotic syndrome is frequently associated with hypocomplementemic glomerulonephritis, an assessment of the effect of the syndrome per se on level of various components is of importance (Frederic Strife, 1986).

West and Ogg suggested that persistent hypocomplementaemia is characteristic of a discrete group of patients with poorly selective proteinuria. None of MCNS had
hypocomplementemia. 3 cases out of 33 had low C₃ levels initially in MCNS group.

Seven out of 8 had low C₃ levels initially in mesengial proliferative group and 3 cases had persistently low levels, while membranoproliferative glomerulonephritis had 5/6 patients initial low levels and 3/6 having persistently low levels. In membranous group, only 1/3 had low levels initially but none had persistently low levels.

Mehta and Ali (1985) reported that serum complement levels are generally normal in MCNS although indirect evidences of complement activation have been reported by Hoyer (1982).

Serum complement levels were never found lower than 85% mg% by Mehta and Ali (1985).

No definite role for circulating immune complexes has been established (Hoyer, 1982).

DEFINITIONS

1. **ISKDC Criteria**: Generalised swelling, proteinuria >40 mg/m²/L, hypoalbuminemia <2.5 gm%, hypercholesterolemia >200 mg%.

2. Sharples (1985) defined it as proteinuria at least 3+ on albuminstix testing with oedema and a plasma albumin concentration of 25 g/l or less.

3. Meadow et al (1981): heavy proteinuria 0.05 g/kg/day, serum albumin <25 g/l and variable oedema.
4. O, Koskimies et al (1982) and Saxena et al (1985): proteinuria $\geq 40$ mg/hour/m$^2$ hypoalbuminemia $\leq 2.5$ gm%
age within the range of $\geq 12$ weeks and $\leq 16$ years.

**REMISSION**

No oedema and urine free of protein by qualitative testing for 5 consecutive days (Rance et al, 1976).

**RELAPSE**

- Edema or first morning sample of urine contains $2+$ reaction for 7 consecutive days (Rance et al, 1976).
- Defined as 3 consecutive days of proteinuria measuring $2+$ or more (Tranin et al, 1975).
- Defined as recurrence of proteinuria $3+$ necessitating further steroid treatment.
- Reappearance of proteinuria $\geq 40$ mg/hr/m$^2$ or $2+$ or more for 3 consecutive days.

**FREQUENT RELAPSE**

- Two relapses within 6 months or three within a year even though they respond to daily prednisolone therapy (Rance et al, 1976).
- Those with four relapses per year or two within 6 months of diagnosis.

**RESPONSE**

Decrease in rate of urinary excretion of protein to $\leq 4$ mg/hr/m$^2$ for 3 consecutive days (zero to
traces on bedside urine examination).

**STEROID RESPONSE**

Defined as the abolition of proteinuria within eight weeks of starting treatment with prednisolone with 60 mg/m$^2$/day or 2 mg/kg/day.

Defined as complete remission within 8 weeks of prednisolone therapy, persisting for at least 2 months after termination of therapy (Tejani et al, 1985).

**INITIAL RESPONDER**

Any patient who responded during 8 weeks of initial steroid regimen.

**NON RESPONDERS TO STEROIDS (Steroid resistant)**

A. **Early non responder**
   - Failure to achieve remission with a 4-10 weeks of prednisolone therapy (5-10% of MCNS).
   - Any patient who failed to respond during initial 8 weeks of prednisolone therapy (Tranin et al, 1975).

B. **Late non responder (5% of MCNS)**

Failure to achieve remission with 28 days course of prednisolone after one or more steroid induced remissions. Before labelling the case as non responder, presence of infection is to be excluded (Tranin et al, 1975).
PHASES OF NEPHROTIC SYNDROME

a. Nephrotic phase - Initial episode
   - Relapse

b. Remission phase - Unstable remission
   - Stable remission.

Unstable Remission

Remission requiring steroids for maintenance of disappearance of urinary albumin and normal serum albumin.

Stable Remission

Remission maintained despite withdrawal of steroid.

INFREQUENT RELAPSERS

Patients with less than 3 per year or less than two relapses per 6 months.

STEROID DEPENDENT

In these patients proteinuria recurs when dose of steroid is reduced below a critical level or proteinuria occurring within 2 months after termination of treatment on at least 2 consecutive occasions (Rance et al, 1976).

Veda et al (1990) described it as relapse occurring either by reducing dosage of steroids or within 14 days of discontinuing prednisolone.
STEROID RESPONDERS

Those patients who became urine albumin free within 4 weeks of onset of steroid therapy persisting for minimum 2 months after termination of therapy in dosage of $60 \text{ mg/m}^2/\text{day}$ or $2 \text{ mg/kg/day}$ prednisolone.

These were divided into (a) frequent relapsers and (b) infrequent relapsers.

SLOW RESPONDERS

In whom proteinuria becomes less but did not disappear within 8 weeks of steroid therapy though eventually disappears completely (Vaishnav et al, 1983).

FREQUENT RELAPSES WITH STEROID DEPENDENCY

In whom two consecutive relapsers or 2 out of 4 relapses in any 6 months period occurred after the prednisolone dosage was given for previous relapse had been reduced from daily to intermittent or alternate day schedule or within 14 days of discontinuing a course of steroid therapy (Arbeit gemin Schaff).

Tejani et al (1985) defined it as proteinuria recurring within 2 months after termination of treatment on at least 2 successive occasions.

FREQUENT RELAPSES WITHOUT STEROID DEPENDENCY

Patients with 2 or more relapses within 6 months of initial response or 4 or more relapses within any 12 months period (ISKDC, 1974).
REMISION TIMES

Interval from day one without proteinuria to first day of subsequent significant proteinuria.

MEAN RELAPSE FREE INTERVAL

Number of days for which patient remains free from proteinuria.

RESPONSE TIME

Defined as interval between the initiation of treatment and first day of reduction of proteinuria to a negative or trace dipstick reaction obtained for at least 3 days.

REMISION ON CYCLOPHOSPHAMIDE

Tejani et al (1985) defined as complete loss of proteinuria persisting for at least 6 months. The longer time period for defining a remission on cyclophosphamide as compared to prednisolone is based on the premise that a more toxic drug should be used if greater benefit is derived.

LATE NON-RESPONDERS TO STEROIDS

The late occurrence of steroid resistance cannot be predicted, because various clinical and laboratory features at the onset of nephrotic syndrome as well as the early course in such patients may not differ from those in the larger group who remain steroid sensitive (Srivastava, 1984).
Incidence of late steroid resistance to cortico-steroids therapy in patients who initially respond is difficult to estimate because the issue has seldom been addressed. In single report (Trainin, 1975) incidence was 5%. Grupe (1979) suggested it as 4.8%. Srivastava et al (1986) estimated the incidence of late steroid resistance approximately 3%.

Trainin et al (1975) reported 10 patients with late non response to steroids, all with minimal lesions. Of these 7 responded to cyclophosphamide but 5 of them again relapsed.

Occurrence of late steroid resistance is unusual and that such patients have minimal lesions additionally they begin to respond to treatment with cyclophosphamide or chlorambucil and subsequently again become steroid responsive.

Late steroid patients comprise of heterogenous group. Those with focal segmental glomerulosclerosis and resistant to cyclophosphamide therapy may have poor outcome.

**TUBERCULOSIS AND NEPHROTIC SYNDROME**

Children with nephrotic syndrome are prone to infections. Since tuberculosis is one of the infections commonly seen in children in India, children with nephrotic syndrome may also have or develop tuberculosis. Of 380 cases of nephrotic syndrome, 10% had evidence of
tuberculosis, 34 males and 4 females (Vaishnav et al, 1983). This was four times higher than the incidence of tuberculosis in pediatric age group (2.7%). Children with the age of onset of nephrotic syndrome 7-9 years had higher incidence of tuberculosis as compared to other age groups. 5.4% had tuberculosis earlier and 5.5% developed tuberculosis after the use of steroids. MCNS was biopsy proved in 73.6% cases in tubercular group and 89.5% in non tubercular group.

Response of nephrotic syndrome to steroid in presence of tubercular infection was slow. So any of nephrotic syndrome patient having slow response should be investigated for tuberculosis in addition to other infections.

RECOGNITION OF FREQUENT RELAPSAERS

If one is certain about immunopathological mechanisms working in MCNS, one may try and see if there be any differences in MCNS frequent relapser and infrequent relapser. It is known over the course of years that 85% cases of MCNS responded and under go remission on cortico-steroid therapy. Of the initial responders, 24% do not relapse and 22% get infrequent relapses. However, 53% of responders are frequent relapsers (Grupe, 1979) about 1/3 patients have no relapse or one relapse.

The most difficult problem in case of children with MCNS continues to be occurrence of frequent relapses in patients who respond initially to treatment with steroids. Repeated or continuous administration of steroids
although usually effect is frequently associated with severe toxicity (ISKDC, 1982).

Preventing the occurrence of frequent relapses and until that is possible, finding more effective and safer methods of treating them remains the major unsolved problem in the case of patients with MCNS. Attempts to correlate the course of disease with histologic findings findings have not only with limited success (ISKDC, 1982).

In report of ISKDC (1982) analysis was made of clinical course of 218 responsive children with MCNS during 2 years period following initial response to prednisolone therapy. No correlation was found between the frequency of relapse and :-

1. Histopathologic subgroups of MCNS.
2. Clinical and laboratory characteristics observable at the time of diagnosis.
3. The time of initial response.
4. Interval between initial response and first relapse.

**CLINICALLY**

Number of relapses that occurred during first 6 months was highly predictive of the subsequent course of 99 children who had no relapse during first 6 months, 93 had fewer than 3 relapses during subsequent 18 months and only one had more than 6 relapses. In contrast, 37 cases who had 3 or more relapses during first 6 months, 17 had < 6, 13 had > 10 and only 7 had ≤ 3 relapses. So it
proves that course of nephrotic syndrome during first 6 months can predict the likely course regarding identification of frequent relapsers.

ISKDC (1982): Absence of relapse during first 6 months following the initial response proved to be an excellent clinical predictor of a favourable course during first 2 years. In contrast, occurrence of 3 or more relapses during initial 6 months period can be used clinically to predict and frequently relapsing course. Fifty percent of children who had 3 or more relapses in first 6 months will continue to have frequent relapses.

Contrary to reports by Cornfield and Stewart (1966), Arneil and Lam (1966) Seigel et al (1972), presence of hematuria, transient azotemia or hypertension at the time of diagnosis did not correlate with the frequency of relapses during first 2 years.

HISTOPATHOLOGICALLY

ISKDC (1982)

Presence of either mild mesangial proliferation or focal tubular changes on renal biopsy is associated with a decreased rate of initial response but not with an increased frequency of relapses. At present therefore potential frequent relapsers cannot be identified from histopathological characteristics.

Saxena et al (1985) after studying clinical feature and correlating them with histopathological examination inferred that majority of patients having
mesengial alterations like mild mesengial thickening, mild mesengial hypertrophy and focal glomerular obsolescence belong to non responders, steroid dependent and frequently relapsing group.

ISKDC (1981) divided minimal lesions on light microscopic examination into 5 subtypes and tried to correlate these subtypes with steroid response:
1. Nil diseases.
2. Minimal mesengial thickening.
3. Focal glomerular obsolescence.
4. Focal tubular changes
5. Minimal mesengial hypercellularity.

A higher proportion of initial non responders were among group with focal tubular changes and minimal mesengial hypercellularity. There was no difference in number of frequent relapses in each group.

IMUNOLOGICALLY

Andal et al (1990) described differences in IgG and IgM in frequent relapsers and infrequent relapsers. Levels of IgG were significantly low and IgM high in frequent relapsers and remained so in remission as compared to infrequent relapsers. Thus persistently low levels of IgG may be a pointer towards frequent relapser, children with frequent relapsers were found to having very low IgG levels at onset.
Some groups have shown high mesangial cellularity and immune complex deposits in frequent relapers. So low IgG and abnormal histology, immunopathology may indicate that the patients could be a frequent relapser.

Giangiocoma (1975) and Glassock (1986) reported no change in immunoglobulin levels between frequent and infrequent relapers.

According to study by Andal et al (1990) very low levels of IgG at onset may serve as a marker for early identification of frequent relapers.

SYMPTOMATOLOGY
Age of onset

Sixty percent of the cases of MCNS variety fall between 2-6 years of age. Though it is reported before 1 year and adult age. In a study by Saxena et al (1988), mean age of onset for MCNS was found 5.899±3.462, 9.857±2.795 years for FSGS, 9.556±1.740 years for membranoproliferative glomerulonephritis and 7.600±1.949 years for membranous nephritis. Sixty six children studied in this group showed mean age of 7.5 years at the time of initial presentation.


Paul and Enery (1982) ; Though nephrotic syndrome can present at any age but 74% of children with MCNS have onset of their disease between 2-7 years with a male ;
female ratio of 2:1. In adolescence and adults, this sex ratio is almost 1:1.

Rance et al (1976) Most children with MCNS present between 1 and 6 years of age. Earlier onset of nephrotic syndrome especially under 3 months of age, is more likely in patients with underlying disease. Male: female ratio is 2:1. While focal glomerular sclerosis can present at all ages. Male to female ratio was 3:2 (Habib et al, 1972).

In MPGN lesion usual age of onset was found to be between 6-16 years. female to male ratio was 1:1. It is commonest lesion in second decade of life (Habib et al, 1972).

In membranous nephropathy usually the patients were between 1 to 14 years of age. Male to female ratio was 3:1. It was the most common cause of nephrotic syndrome in adults(Habib et al, 1972). In nephrotic syndrome due to post streptococcal glomerulonephritis, age of onset was usually after 3 years. i.e. school going age.

EDEMA

This is the commonest presentation of nephrotic syndrome. Edema is soft pitting, usually starting as periorbital and slowly progressing to dependent parts of body and then generalized. In its course ascites and pleural effusions usually occur. Edema can be periorbital pretibial, pedal, anterior abdominal wall, scrotal, or labial involving perineum.
Periorbital swelling is more prominent in the morning, subsiding throughout the day. Whereas ankles become progressively was more common. Facial swelling can be misdiagnosed as allergic reaction and weight gain due to edema can be falsely interforated as a sign of good health. Edema is the hall mark of presenting features of nephrotic syndrome.

Oedema formation was defined by Bohlin (1984) as weight gain during 3 days preceding the study and more than 0.6% weight gain of the body weight per day.

**OLIGURIA**

Oliguria is presenting complaint, usually along with edema. It is due to hypovolemia which is in turn due to fall in plasma oncotic pressure due to loss of albumin. Urine is opalescent due to lipiduria.

**HEMATURIA**

Gross hematuria is quite rare in minimal lesion of nephrotic syndrome. It was reported in 13% of MCNS cases by White (1971).

Gross hematuria is rare in MCNS though it can be present microscopically (Habib et al, 1973).

Habib et al (1973) reported microscopic hematuria in 66% cases of FSGS, 68% in MPGN while gross in 20% while in 70% cases of membranous nephropathy while 20% of these patients presented with gross hematuria.

Microscopic hematuria was reported to occur in 13 to 29% at the time of diagnosis by Lagrue et al (1975)
and habib et al (1971), while gross hematuria was reported to be in only 1.4% of cases. Saxena et al (1988) showed presence of hematuria in 40% patients among non responders. Microscopic hematuria is commonest in patients with FSGS and is presenting feature in 50 to 90% of cases (Cameroon, 1966; 1973; Glassgow, 1971). Bohlin (1984) reported that none of their 23 patients of MCNS had persistent hematuria.

**HYPERTENSION**

It is uncommon in idiopathic nephrotic syndrome. It was reported in 9% cases by White (1971). It is present in 6-13% children with MCNS and usually mild and normal (ISKDC, 1982). Habib et al (1973) reported hypertension in 10% cases of FSGS in 25% in M\(\text{PGN}\) and in 5% cases of membranous nephropathy.

Saxena et al (1988) reported hypertension in 35.5% cases of non responding type. Majority of the patients presented with headache, swelling, nausea, vomiting and poor appetite.

Sonja Kuster et al (1990) reported that in MCNS 95% of children with nephrotic syndrome had hypertension prior to steroid treatment in edematous phase (B.P. 795% percentile of age). After complete remission, the prevalence of hypertension decreased to 19%. In FSGS prevalence of hypertension was 91% and 24% after remission.

They concluded that irrespective of age, hypertension is a common feature of nephrotic syndrome unrelated to steroid therapy or renal failure.
Bohlin et al (1984) studied 23 children aged 2 to 15 years of MCNS (Biopsy proved 21) and reported none of them had hypertension.

**AZOTEMIA**

Saxena et al (1988) reported azotemia in 28% cases of idiopathic nephrotic syndrome.

**DIARRHOEA AND ABDOMINAL PAIN**

Diarrhoea and abdominal pain is usually present in intestinal wall oedema and requires no treatment.

**DIFFERENTIATION OF MCNS FROM OTHER ASSOCIATED DISEASES WITH NEPHROTIC SYNDROME**

Early differentiation of patients with MCNS from those nephrotic syndrome associated with focal glomerular sclerosis or other forms of chronic or acute nephritis is of prime importance.

Manifestations that favour a diagnosis of MCNS are absence of azotemia, hypocomplementemia, hypertension, hematuria and age 1 to 6 years. These features, except for hypocomplementemia may be found in 10-20% of children with MCNS (Habib et al, 1971; ISKDC, 1978 and White, 1970).

These features are much commoner, especially when present in combination, in patients of nephrotic syndrome caused by other than MCNS.

Even though these clinical features may be helpful the most accurate and non-invasive discriminator of glomerular disease causing nephrotic syndrome is the child's

Of the total 471 nephrotic syndrome patients who responded to prednisolone, 92% had MCNS proved by renal biopsy (ISKDC, 1981).

Ninety three percent cases of 363 patients proved to be MCNS by biopsy among those who responded to initial 8 weeks of prednisolone treatment with complete loss of proteinuria.

Clinical features that suggest the syndrome may be due to a histologic lesion other than MCNS include:

1. Children less than 9 months of age.
2. Persistent hematuria.
3. Heme or red cell casts in urine.
4. Low serum complement.
5. Azotemia

In absence of these signs, it should be assumed that child is having MCNS (Cameroon, 1968).

LAB DIAGNOSIS

24 hour and bed side urinary protein analysis

Urine normally contains small amount of protein however, sensitivity of standard diagnostic test is adjusted so that this is not detected.

Nephrotic syndrome is characterized by massive proteinurinia and nearly all clinical and biochemical changes are due to such heavy proteinurinia. It is the single most diagnostic clinical laboratory finding in patients with nephrotic syndrome.
The upper limit of normal proteinuria in children is not well defined, but is probably in the order of 100 mg/m²/hour.

Protein excretion in excess of 200 mg/day is definitely abnormal either in child or an adult.

Abramovicz et al (1970); ISKDC defined nephrotic proteinuria as 740 mg/m²/hour.


- Physiologic < 0.1 g/m²/day
- Intermediate 0.1 and < 1 g/m²/day
- Nephrotic > 1.0 g/m²/day

Cameroon (1968) and James defined massive proteinuria as urinary protein exceeding 50-100 mg/kg/day.

Saxena et al (1988) found that 60% patients under 6 years of age (mean 5.8 years) of MCNS presented mainly with proteinuria.

Bed side diagnosis of massive proteinuria is made by 4+ reaction by heat acetic acid test.

**PROTEIN SELECTIVITY INDEX (SPI)**

SPI is defined as the ratio of urine to serum concentrations of a large molecular weight. Serum protein (IgG or transferrin) divided by simultaneously measured ratio of urine to serum concentration of albumin multiplied by 100.

\[ SPI = \frac{\text{Urine IgG/Plasma IgG}}{\text{Urine albumin/plasma albumin}} \times 100 \]
This technique defines the relative permeability of the GBM to serum proteins of different molecular weights when the proteins of larger molecular weight pass the glomerular filter, the higher is the SPI, worst is the prognosis. In MCNS, SPI remains \( \leq 4 \). In membranous and proliferative nephropathies SPI is usually more than 0.2 and predicts a poor response to steroids and guarded prognosis.

**Serum Albumin**

Marked hypoalbuminemia is one of the major characteristics of nephrotic syndrome with serum albumin usually \( \leq 2.5 \text{ gm}\% \) or low.

**Serum Cholesterol**

This is considered when serum cholesterol levels are more than 200 mg\%. From the practical standpoint, plasma cholesterol levels become elevated as serum albumin concentrations drop below 1 g\% and of triglycerides when serum albumin falls below 1 gm\% (Baxter et al, 1960).

**Blood Urea and Serum Creatinine**

Elevation of serum creatinine and blood urea nitrogen are initially present in approximately 25% of children with MCNS (White et al, 1970; ISKDC, 1978).

Saxena et al (1988) reported that 28% cases of idiopathic nephrotic syndrome had azotemia.
URINE OSMOLALITY

Patients with nephrotic syndrome had impaired concentrating capacity evidenced by low urinary osmolality. Serum albumin levels do not affect urine osmolality. But patients with clinically severe disease had more severe impairment of urinary concentrating capacity (UCC). Normal levels of urinary osmolality after an overnight fast is 800-1300 m Osm/kg.

Date and Kaushik et al (1990) reported severe impairment of UCC in patients with clinically severe disease i.e. frequent relapses. They reported urine osmolality $432.10 \pm 125 (115-690)$ while in controls it was $798.5 \pm 81.7 (710-960)$.

DIAGNOSIS OF NEPHROTIC SYNDROME

It was made on basis of characteristic clinical history of oedema, laboratory findings of heavy proteinuria more than 50/kg/day or more than 40 mg/m$^2$/hour hypoalbuminemia $\leq 2.5$ gm% and hypocholesterolemia $\leq 200$ mg%.

Diagnosis of steroid responsive nephrotic syndrome was made on basis of absence of contradictory features like hypertension, persistent hematuria, persistent azotemia and hypocomplementemia. ISKDC laid down following criteria for selection of patients of idiopathic nephrotic syndrome.

1. Heavy proteinuria $\geq 40$ mg/m$^2$/hour determined quantitative on 24 hour urine collection.
2. Hypoalbuminemia \( \geq 2.5 \) gm%.
3. No evidence of underlying systemic disease or exposure to agents known to be associated with nephrotic syndrome.
4. Age 712 weeks and \( \geq 16 \) years at the time of diagnosis.

**MANAGEMENT**

**Steroids**

Steroids are the mainstay of treatment of idiopathic nephrotic syndrome. Various regimens are being followed for the treatment of nephrotic syndrome.

**Long term daily therapy**

Initial dose of prednisolone 2 mg/kg/day in divided doses for 1-3 months followed by a tapering dose schedule during 3-6 months by decreasing the dose by 5 mg/day on alternate day.

**ISKDC (1976)**

a. To *induce remission* (daily prednisolone therapy):
   20 mg/kg/day (maximum 80 mg/day) in 3-4 divided doses until the urine is protein free for 5 days (maximum duration of 28 days), if remission does not occur within 28 days intermittent therapy is started at 4 mg/kg (maximum 120 mg) with break fast up to 28 days on alternate days.

b. To *maintain remission* (Intermittent therapy):
   1) 2.0 mg/kg/day (Maximum 80 mg) with breakfast on
alternate days for 20 days. It is then gradually reduced over 2-4 months by 10 mg decrements to 30 mg and then by 5 mg decrements until discontinued.

ii) 2 mg/kg/day in 3-4 divided doses on 3 consecutive days each week for 4 weeks. It is then gradually reduced over 2-4 months until discontinued.

**Standard intermittent therapy**: (ISKDC, 1979)

Start the initial dose of prednisolone 60 mg/m²/day (maximum 80 mg) in divided doses daily till remission is obtained then 40 mg/m²/day of prednisolone given in divided doses on 3 consecutive days out of 7 for a period of 4 weeks.

**Short term daily therapy** (Arbeits geinmeischaf, 1981):

Initial regimen with 60 mg/m²/day immediately after remission treatment with prednisolone was discontinued.

**Standard alternate day therapy** (Brodehl et al, 1982):

Start initial dose of 60 mg/m²/day in divided doses till remission is obtained then 40 mg/m²/day as single morning dose alternate day for 4 weeks.

**ISKDC (1982)**

Initial treatment - 60 mg/m²/day maximum dose 80 mg/day in divided doses for 4 weeks followed by 40 mg/m²/day in divided doses for 3 consecutive days out of 7 for 4 weeks. Treatment/relapse is the same.
Srivastava et al

Start with prednisolone 2 mg/kg/day in 4 divided doses for 4 weeks followed by same dose alternate day for another 4 weeks.

Each relapse to be treated with 2 mg/kg/day prednisolone until proteinuria abolished maximum for 4 weeks followed by same dose alternate day for 4 weeks.

Veda et al (1990)

Initial episode of the nephrotic syndrome were treated with prednisolone in divided doses of 60 mg/m²/day for 4 weeks with the dose being tapered by 5-10 mg/m² every two weeks during next 3-4 months.

Those patients who had milder degrees of proteinuria (74 mg/m²/hour but ≤40 mg/m²/hour) were managed with previous maintenance dose of prednisolone for 1-2 weeks, the dose either being increased to 60 mg/m²/day if remission (≤4 mg/m²/hour proteinuria) was not achieved.

Patients who respond to initial prednisolone medication with two consecutive days of protein free urine have their regimen of prednisolone switched to an alternate morning schedule of 2 mg/kg alternate morning schedule maintenance dose is continued for 1 month and then decreased to 1 mg/kg for a second month and finally decreased and discontinued in third month of follow up. (ISKDC, 1982 ).
**Treating a relapse**

Follow up alternate morning prednisolone is continued in a slow decreasing dosage over 6-12 months before being discontinued. Alternate day regime is reported to be more effective in preventing disease relapse and has less steroid toxicity in comparison to intermittent regimen suggested by ISKDC.

Some workers of German pediatric nephrology group recommended a low dose prednisolone 35 mg/m²/day every alternate day for 40 weeks after response is induced by 60 mg/m²/day initially in a frequently relapsing patient. Alternate day therapy with low dose keeps patient tree of relapses and also minimises steroid toxicity.

Feehally and Kendall defined MCNS as steroid responsive nephrotic syndrome (complete abolition of proteinuria within 4 weeks in response to corticosteroid treatment) with no hypertension or renal impairment. In some cases there was further information from percutaneous renal biopsy.

Siegel et al (1987) reported that frequently relapsing steroid responsive childhood nephrotic syndrome is assumed to have MCNS morphology based on clinical course. It has been reported that frequently relapsing children maintained on alternate day regimen relapsed less often than those treated for 3 consecutive days per week. How a difference in the maintenance regimen might have
affected the results reported cannot be determined.

An early frequently relapsing course should not be considered an automatic indication for instruction of treatment with drugs other than prednisolone. Since 50% of patients having 73 relapses in first 6 months had relatively few relapses in subsequent 18 months and those who did relapse frequently showed little or no evidence of steroid toxicity a alternate day regime.

Rance et al (1976) reported alternate day method cause less cushingoid obesity and hypertension.

Polito et al (1986) reported that alternate day regimen did not affect statural growth and bone maturation of children with lipid nephrosis. Only one of 20 children treated for 1 year last 0.5 SD.

Rees (1990) suggested that alternate day treatment may minimize growth retardation and leave final height unaffected.

It has been observed that when a patient responds to corticosteroids initially, he would generally continue to do so even if he is a frequent relapsrer. He may become steroid dependent but over all he responds to steroids every time he gets a relapse.

Uncomplicated child with nephrotic syndrome who is over the age of 1 but under the age of 7 years, has a normal C3 concentration and does not have gross hematuria,
probably has MCNS and should be given a therapeutic trial with prednisolone. If histologic diagnosis is one of proliferative forms of disease, membranous nephropathy, or advanced glomerular sclerosis, steroid therapy appears to be ineffectual and may cause hypertension or other complications. Children with age 7 and <6 years having gross hematuria and hypertension are more likely to have disease other than MCNS.

ISKDC has shown that all nephrotic children who are going to respond to prednisolone 73% did so within 14 days and 94% within 28 days of initiation of the daily divided dose.

In patients who at the end of 4 weeks are still nephrotic or still have 1 to 2+ amounts of proteins renal biopsy should be performed. Within these criteria very few children with MCNS will need a renal biopsy.

**MANAGEMENT OF CHILDREN WITH FREQUENT RELAPSES/STEROID DEPENDENCE**

Twenty five percent of MCNS exhibit frequent relapses (ISKDC, 1974). In such patients, treatment line is controversial use of alkylating agents is recommended in such cases by Clim et al (1973), Garin et al (1978), Grupe et al (1973). But there are potential side effects of such agents and visual long term prognosis in patients with MCNS. Paul and Eneny (1982) attempted to suppress relapses with long term alternate day prednisolone.
Maintenance with 1.4 mg/kg alternate day of prednisolone is usually not associated with significant steroid toxicity and is acceptable alternative to use of alkylating agents.

ROLE OF CYCLOPHOSPHAMIDE

Adequate controlled trials have shown that cyclophosphamide used in combination with steroids will decrease the rate of relapse in children who have steroid responsive frequently relapsing syndrome.

Usual regimen is 2 to 3 mg/kg/24 hours for 8 weeks. Sixty five percent patients remain in remission after 5 years of treatment. Permanent remission was reported in 50% cases. Response to cyclophosphamide may be predictable from the pattern of response to steroid therapy. Of those who relapse immediately after tapering steroids, 2/3rds also relapse quickly after cyclophosphamide is also true.

Cyclophosphamide used in combination with steroids will decrease the rate of relapse in children who have steroid responsive frequently relapsing syndrome (Seigel et al, 1981).

Tejani et al (1985) studied efficacy of cyclophosphamide in 39 steroid sensitive frequently relapsing nephrotic syndrome. It was used due to heavy steroid dependence and steroid toxicity. Hundred percent of patients with MCNS responded to cyclophosphamide but only
1 of 15 FSGS patients responded. They suggested that cyclophosphamide should not be used in patients whose disease has evolved from MCNS to FSGS.

Ueda et al (1990) treated 32 patients with cyclophosphamide for 8 weeks and 41 for 12 weeks. The relapse free rate of patients treated for 8 weeks (25%) was similar to that of treated for 12 weeks (24%). They conducted that cyclophosphamide should no longer be used longer than 8 weeks at a dose of 2 mg/kg/day in children with MCNS.

Moncrief et al (1969) and Chiu et al (1973), in well controlled trials showed high dose leukopenic regimen combined with low dose prednisolone is effective in reducing the frequency of relapsing disease and lengthening the interval between relapses of proteinuria.

Following 90 day course 75% children did not have a relapse within 1 year of treatment and 50% did not relapse for 2 years.

Paul and T. Mc Enery (1982) suggested 2.0 to 2.5 mg/kg/day in conjunction with small daily dose of prednisolone for 8-16 weeks.

Alopecia, leukopenia, hemorrhagic cystitis, infection have to be looked for it also affects gonadal function.

CHLORAMBUCIL

Clinical trials with chlorambucil are recent.
It has advantage of fewer toxic side effects and fewer relapses when compared to cyclophosphamide.

Grupe et al (1976), Baluarali (1978) and Callis et al (1980) recommended the dose 2 mg/kg/day for 5-15 weeks in combination with low dose prednisolone. This yeilded continuous remission rate in 95% children, 1 year after combined therapy and in 85% after 3 years combined therapy (Williams et al, 1980)

Seizures was a a problem but other toxic effects of cyclophosphamide were less.

MANAGEMENT OF STEROID RESISTANT MCNS

It carried a poor prognosis and 80% progress to end stage renal disease.

Ciclosporin

It is a powerful immunosuppressive agent. (Patrick Niaudet (1991) suggested that ciclosporin in combination with prednisolone may be efficient in patients with steroid resistant nephrotic syndrome with either MCNS or FSGS.

Dose recommended is 150-200 mg/m²/day combined with daily prednisolone 30 mg/m² for 1 month and with alternate day prednisolone 30 mg/m² thereafter for 5 months.

Meyrier et al (1986) showed ciclosporin-A may be effective in treatment of patients with nephrotic syndrome that resist every other form of treatment and especially in those with lipoid nephrosis.
Peter Hoyer (1980) reported that cyclosporin was effective in MCNS patients resistant to steroids and cyclophosphamide, in severe steroids dependent MCNS. Dosage administered were 100-200 mg/m²/day along with alternate day. They found that relapse rate reduced considerably and even resistant cases responded.

Though its extensive use is still not done, caution trials are recommended.

MANAGEMENT OF PATIENTS WITH MESENGIAL PROLIFERATION NEPHROTIC SYNDROME

2.3-5.3% of patients of nephrotic syndrome will have this lesion on renal biopsy. Clinically these patients are not distinguishable from MCNS. Mean age and older and incidence of macro-microscopic hematuria is higher (36-100%). Fifty percent respond to usual steroid therapy and 25% to immunosuppressive therapy.

MANAGEMENT OF FSGS

Importance of this lesion is, relative cortico-steroid resistance and progression to end stage renal disease as described by Churg et al in report for ISKDC (1970). Seventeen percent of biopsy proven FSGS patients respond to steroids but usually have frequent relapses. This group comprise 40% of all cases which are steroid resistant (Nash et al, 1976). Modes of treatment are azothiaprine, dipyridamole, aspirin.
Steroid resistance cases have poorer prognosis. Overall 50% survive from 3 to 16 years.

MANAGEMENT OF OEDEMA

Diuretics are not indicated unless ascites or pleural effusion are distressing to the patients. Major complication of diuretic therapy is hypokalemia.

a. **Salt restriction**: Salt should be restricted to 0.5- to 1 gm/day till oedema subsides.
b. **Salt poor albumin**: 0.5-1 g/kg over 60 minutes followed by I/V furosemide.

HYPERTENSION

Following diuresis, blood pressure usually becomes normal. Otherwise hydralazine can be used intravenously or oral 0.7 mg/kg/day in 4 divided doses. Intravenous diazoxide in acute emergency, it can be increased to 200 mg/day.

SUPPORTIVE CARE

- Normal ambulation should be maintained.
- Infections should be treated accordingly.
- No dietary restriction except low salt diet is indicated in uncomplicated case.

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