Introduction
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1.1 The Historical background

The term “Nephrotic Syndrome” describes the clinical state characterized by the presence of Proteinuria, Hypoalbuminemia, and Edema. Although other clinicopathological findings co-exist with the abovementioned three clinical state characteristics, they remain the central findings in Nephrotic Syndrome. Both Edema and Proteinuria have been clinically known for nearly 2000 years. In 1827, Richard Bright first demonstrated that Edema and Proteinuria were dependent on changes in the kidney and for the next 80 years, Nephrotic Syndrome was known as “Bright’s disease” (Cameron J.S., 1988). In 1905, Friedrich Von Muller further delineated kidney diseases into “Nephritis” and “Nephrosis”, and finally in 1929, Henry Christian included the phrase “Nephrotic Syndrome” in his writing (Cameron J. S., 1988).

Whereas the name “Nephrotic Syndrome” took millennia to emerge, its clinical course had been known for some time. Although many patients died due to this disease, many physicians knew that Edema might be cured or even remit spontaneously (Cameron J. S., 1988). Once effective treatment for the Nephrotic Syndrome was available, it became apparent that not all patients responded to therapy.

1.2 Definitions

According to Clark A.G (1998), Nephrotic Syndrome requires the presence of Edema, Hypoalbuminemia less than 2.5 g/dl and Proteinuria greater than 40 mg/m²/h or a protein to creatinine ratio greater than 200 mg/mmol (or 2.0 mg/dl/mg/dl).

Remission: Denotes a reduction of the Proteinuria to less than 4 mg/m²/h or a urinary albumin dipstick of 0 or trace for 3 consecutive days.

Relapse: It occurs with the recurrence of Proteinuria of greater than or equal to 40 mg/m²/h or a urinary albumin dipstick of 2+ or greater.
**Steroid Responsive:** Those patients who go into remission with steroid therapy alone are called Steroid Responsive (or sensitive).

**Steroid Resistant:** Those patients in whom remission is not achieved after 8 weeks of steroid therapy are labeled as “Steroid Resistant Nephrotic Syndrome” (SRNS).

According to Indian pediatric nephrology group (2001), Nephrotic Syndrome is characterized by heavy Proteinuria Hypoalbuminemia (serum albumin less than 2.5 g/dl), Hyperlipidemia (serum cholesterol greater than 200 mg/dl) and Edema.

According to Mitarai T. (2004), Nephrotic Syndrome is defined as the Glomerular disease with massive Proteinuria, Hypoalbuminemia and numerous complications. Among these complications saltwater retention, hyperlipidemia, metabolic bone disease, thromboembolism and infections are most important for management of Nephrotic Syndrome.

According to Bagga A. *et al.*, (2005), various Nephrotic Syndrome related terminologies are described as:

**Nephrotic Syndrome:** Presence of Edema, Nephrotic range Proteinuria (greater than 40 mg/m²/h on timed sample, spot albumin to creatinine ratio greater than 2 mg/mg); hypoalbuminaemia (less than 2.5 g/dl).

**Relapse:** Urinary protein excretion greater than 40 mg/m²/h; Proteinuria by dipstick greater than 3+ for 3 consecutive days.

**Remission:** Urinary protein excretion less than 4 mg/m²/h; nil or trace by dipstick on spot sample for 3 consecutive days.

**Frequent relapses:** Two or more relapses in 6 months of initial response; 4 or more relapses in any 12 month period.

**Steroid dependence:** Occurrence of 2 consecutive relapses during steroid therapy or within 2 weeks of its cessation.
Steroid resistance: Failure to achieve remission after 4 week of daily therapy with oral prednisolone at a dose of 2 mg/kg/day.

According to Bagga A. (2008), various Nephrotic Syndrome related terminologies are described as:

Remission: Urine albumin nil or trace, (or Proteinuria less than 4 mg/m²/h) for 3 consecutive early morning specimen days.

Relapse: Urine albumin 3+ or 4+ (or Proteinuria greater than 4 mg/m²/h) for 3 consecutive early morning specimen days, having been in remission previously.

Frequent relapses: Two or more relapses in 6 months of initial response; more than 3 relapses in any 12 months.

Steroid dependence: Two consecutive relapses when on alternate day steroids or within 14 days of its discontinuation.

Steroid resistance: Absence of remission despite therapy with daily prednisolone at a dose of 2 mg/kg/day for four weeks.

Stoycheff N. et al. (2009) defined Nephrotic Syndrome as urine total protein excretion greater than 3.5 gm/day or total protein-creatinine ratio greater than 3.5 gm/gm, low serum albumin level, high serum cholesterol level and peripheral Edema.

1.3 Diagnostic criteria for Nephrotic Syndrome

Nephrotic Syndrome results from Proteinuria greater than 3.5 grams per day and is characterized by Edema, Hyperlipidemia, Hypoproteinemia, and other metabolic disorders. In addition to primary (idiopathic) glomerular diseases, the Nephrotic Syndrome may be secondary to a large number of identifiable disease states. Despite the differences in their causes, the loss of substantial amounts of protein in the urine results in a shared set of abnormalities that comprise the Nephrotic Syndrome (Brenner and Rector 2007).
Hull R.P. and Goldsmith D.J. (2008) suggested the following diagnostic criterion:

- Proteinuria greater than 3-3.5 g/24 hour or spot urine protein to creatinine ratio greater than 300-350 mg/mmol
- Serum albumin less than 25 g/l
- Clinical evidence of peripheral Edema
- Severe hyperlipidaemia (total cholesterol often greater than 10 mmol/l) is often present

1.4 Pathophysiology

Nephrotic Syndrome is defined by heavy Proteinuria due to abnormal increase of glomerular permeability followed by Hypoalbuminemia, Hyperlipidemia and Edema. Disorders of selective size barrier, charge selective barrier, slit diaphragm and circulating permeability factors are thought to be the causes of Proteinuria. Most patients with Nephrotic Edema have primary water retention. Over production and impaired catabolism of lipoproteins are the causes of Hyperlipidemia. Abnormality of coagulation factors is also associated with Nephrotic Syndrome. Nephrotic Syndrome may be primary or secondary to systemic disorders (Togawa A. et al, 2004). The primary abnormality in Nephrotic Syndrome is thought to be loss of a layer of negatively-charged heparin sulphate within the glomerular basement membrane that allows the increased passage of large amounts of low molecular weight anionic proteins during ultrafiltration. However, recent research has shown that the loss of albumin in the urine may not be due to excessive filtration across the glomerular basement membrane as it was previously supposed, it is rather a failure to reabsorb albumin after its ultrafiltration. It appears that renal disease may cause impairment of the ability of cells in the proximal renal tubules to endocytose albumin that has been filtered across the glomeruli, and deliver it back into the blood supply around the renal tubules (Russo L.M. et al., 2007) In acquired and chemically induced kidney disease, albuminuria is the result of dysfunction in proximal tubular cell processing of albumin rather than alterations in glomerular permeability (Comper W.D. et al., 2009).
Figure 1.1: The glomerular barrier with the podocyte foot processes at the bottom, the GBM (Glomerular Basement Membrane) and the endothelium with its ESL (Haraldsson B., Nyström J., and Deen W.M., 2008).
Figure 1.2: Certain components of the ESL (Endothelial surface layer) are shown in higher detail. (Haraldsson B., Nyström J., and Deen W.M., 2008)
1.5 Common causes of the Nephrotic Syndrome

It can be caused by a wide range of primary (idiopathic) and secondary glomerular diseases. Generally, the glomerular diseases that cause Nephrotic Syndrome can be divided into primary and secondary etiologies.

Primary Nephrotic Syndrome (PNS), also known as Idiopathic Nephrotic Syndrome (INS), is associated with glomerular diseases intrinsic to the kidney and not related to the systemic causes. The sub-categories of INS are based on histological descriptions. A wide variety of glomerular lesions can be seen in INS. These include Minimum Change Nephrotic Syndrome (MCNS), Focal Segmental Glomerulosclerosis (FSGS), Membranous Nephropathy (MN), Membranoproliferative Glomerulonephritis (MPGN), diffuse mesangial proliferation and others. INS is divided into steroid-sensitive (SSNS) and Steroid-Resistant Nephrotic Syndrome (SRNS), because response to steroids has a high correlation with histological subtype and prognosis. The landmark study of Nephrotic Syndrome in children, i.e. the International Study of Kidney Disease in Children (ISKDC), found that the vast majority of preadolescent children with INS had MCNS on kidney biopsy. Whereas 90% of children with MCNS responded to corticosteroid treatment with remission of their Nephrotic Syndrome, only 20% of children with FSGS responded to steroids.

Primary renal diseases which are the most common cause of NS in adults are Idiopathic Membranous Nephropathy (40%) and Focal Segmental Glomerulosclerosis (20%). In these conditions, less than 10% progressed to End Stage Renal Disease (ESRD). Persistent Proteinuria is not only a marker of irreversible glomerular lesions but also a marker of tubulointerstitial lesions, and plays significant role in progression into ESRD (Saito T., 2004).

Following are the causes of secondary renal diseases:

- Postinfectious causes, e.g. Group-A beta-haemolytic streptococci, TB, malaria, syphilis, viruses such as VZV, HBV, HIV, infectious mononucleosis (Kawasaki Y., 2004).
Collagen vascular diseases, for example, SLE, rheumatoid arthritis, polyarteritis nodosa, Henoch-Schönlein purpura, vasculitides.

Metabolic diseases, for example, diabetes mellitus, amyloidosis (Kawasaki Y, 2004).

Inherited disease, for example, Alport's Syndrome, hereditary nephritis, sickle cell disease.

Malignant disease, for example, multiple myeloma, leukaemia, lymphoma, carcinoma of breast/lung/colon/stomach.

Medications, for example, NSAIDs, captopril, lithium, gold, diamorphine, interferon-alpha, penicillamine, probenecid and many others.

Toxins, for example, bee sting, snake bites, phytotoxins.

Pregnancy, for example, pre-eclampsia.

Transplant rejection

1.6 Symptoms

In children, facial swelling is a common presenting feature, with periorbital oedema often being the first evidence that something is wrong; oedema may progress to involve the whole body.

Adults tend to present with peripheral oedema affecting the ankles and legs, which may progress to involve the whole body.

Some patients may notice frothiness of their urine.

Hypercoagulability may manifest as venous or arterial thrombosis, for example, DVT, MI.

Recurrent infections and/or general fatigue, lethargy, poor appetite, weakness or episodic abdominal pain may cause presentation to a doctor.

1.7 Clinical Signs

Nephrotic Syndrome should be part of the differential diagnosis of any patients with new onset oedema. Oedema associated with Nephrotic Syndrome is often first noticed periodically and can become severe. Patients may develop oedema of lower leg and genitals; as well as ascites, pleural effusions and pericardial effusions. Decrease in plasma albumin concentration accompanied by
reduced plasma oncotic pressure is responsible for development of Edema. Urine analysis reveals gross Proteinuria. Hypertension and Haematuria are not usually found but may affect a minority of cases (Hull R.P., 2008). Hypertension may be detected at the onset of Nephrotic Syndrome or latter due to steroids toxicity. Therapy is initiated with Angiotensin converting enzyme (ACE) inhibitor, Calcium channel blockers or β adrenergic antagonists, keeping the blood pressure at less than 90th percentile (Indian pediatr, 2007 and Axelord L., 2006).

1.8 Spectrum of Renal Diseases in Indian Population

In India, Chronic renal failure (CRF), Nephrotic Syndrome (NS), Nephritic Syndrome and hypertension are the four common presentations of renal diseases seen in 47.8%, 15.03%, 4.6% and 4.9% cases respectively. Other presentations are acute renal failure (1.9%), urinary tract infection (2.9%), stone disease (4.6%), obstructive uropathy (2.1%), isolated haematuria (1.2%) and asymptomatic urinary abnormalities (0.3%). Chronic glomerulonephritis is seen in 49.4% cases of CRF followed by diabetic nephropathy in 28.4% cases. In the Nephrotic Syndrome cases, primary glomerulonephritis is seen in 58.5% cases, out of which minimal change disease was the common cause in 38% cases. Of the secondary glomerular diseases, diabetic nephropathy is the commonest cause of NS (53%), followed by amyloidosis (16.4%) and lupus (8.3%). Tuberculosis is the most common cause of renal amyloidosis which is seen in 50% cases. Of the nephritic Syndrome, post-infective glomerulonephritis is the commonest cause followed by rapidly progressive glomerulonephritis being the second most common cause. In the hypertensive group, essential hypertension is the commonest cause followed by renovascular hypertension (Agarwal S.K. et al., 2000).

1.9 Frequency

Nephrotic Syndrome is a relatively rare but important manifestation of kidney disease. In US, its annual incidence among children is reported to be 2–7 cases per 100,000. Incidence varies among adults depending on the incidence of underlying causes for the condition, particularly diabetes mellitus. Nephrotic Syndrome has an incidence of around three new cases per 100,000 each year in adults (CKD guideline, 2008). Diabetic nephropathy with Nephrotic Syndrome is
most common, at an estimated rate of at least 50 cases per million populations. That is an underestimation; however, since the rate of end stage renal disease from diabetes has reached 100 cases per million populations in some Western countries.

In children, Nephrotic Syndrome may occur with a frequency of 20 cases per million children (Wong W., 2007). Biopsy studies in children with Nephrotic Syndrome have shown similar types of histology in India and Turkey, compared with what one would expect in Western countries (Kumar J. et al., 2003 and Ozkaya N. et al., 2004). In Pakistani adults with Nephrotic Syndrome, the spectrum of histologies of kidney biopsies has been found to be similar to that seen in western countries (Kazi I.J. et al., 2007).

1.10 Mortality/Morbidity

➢ In the pre-antibiotic era, infection was a major factor in the mortality rate among patients with Nephrotic Syndrome (Arneil G.C. et al., 1966). Treatments for Nephrotic Syndrome and its complications appear to have reduced the morbidity and mortality once associated with the Syndrome.

➢ In secondary Nephrotic Syndromes, morbidity and mortality are related to the primary disease process, such as diabetes or lupus; although in diabetic nephropathy, the magnitude of Proteinuria itself relates directly to mortality (Jude E.B. et al., 2002).

➢ The prognosis may worsen because of:

➢ An increased incidence of renal failure and the complications secondary to Nephrotic Syndrome, including thrombotic episodes and infection.

➢ Treatment-related conditions, such as infectious complications of immuno-suppressive treatments (Du Buf-Vereijken P.W. et al., 2005).

1.11 Race

➢ Because diabetes is a major cause of Nephrotic Syndrome; American Indians, Hispanics, and African Americans have a higher incidence of Nephrotic Syndrome as compared to white persons.
HIV nephropathy is a complication of HIV that is unusual in whites; it is seen with greater frequency in African Americans (Kopp J.B. et al., 2003).

Focal glomerulosclerosis appears to be overrepresented in African American children as compared to white children, as a cause of Nephrotic Syndrome (Bonilla Felix M. et al., 1999).

1.12 Sex

The ratio of males to females with Nephrotic Syndrome is approximately 2:1 in young children, but this male predilection disappears in teenagers and adults (Clark A.G. et al., 1998, Nash M.A. et al., 1992). There is a male predominance in the occurrence of Nephrotic Syndrome, as there is predominance for chronic kidney disease in general. This male overrepresentation is also seen in paraneoplastic membranous nephropathy (Lefaucheur C. et al., 2006). However, lupus nephritis affects mostly women.

1.13 Age

The image below shows typical ages at which a given cause of Nephrotic Syndrome may occur. It does not show every possible cause of Nephrotic Syndrome, such as lupus nephritis, which typically affects young black women. The ages shown are averages.

average ages of types of nephrotic syndrome

Fig. 1.3: Underlying histological appearances found in renal biopsies from more than 1000 Nephrotic patients of all ages seen at Guy's Hospital 1963-1990.
Note that the majority of children under the age of 15 years have minimal change disease, the proportion falling steadily from 2 to 15 years of age. However minimal changes remain an important cause of the Nephrotic Syndrome in adult Nephrotic; and overall is the most common form. In contrast, Membranous nephropathy becomes steadily more common with age and is the commonest form of Nephrotic Syndrome in elderly patients.

1.14 Sequence of investigation for a person presenting with Nephrotic Syndrome:

No guidelines are available for the investigation of Nephrotic Syndrome. Assessing the patient's renal function is a key part of investigation; serum urea and creatinine should be measured and estimated glomerular filtration rate are calculated. Dipstic testing of the urine for haematuria (which would suggest glomerulonephritis) and Proteinuria (3+ & 4+ protein indicates the Nephrotic range) is essential in measuring the amount of protein loss. A spot early morning urine sample for protein-creatinine ratio or an albumin-creatinine ratio is carried out, as these test are less prone to error, give quicker results, and had been shown in cross-sectional longitudinal studies to be as accurate as 24 hour urine collection (NICE_73_ 2008 Ruggenent P., 1998). A protein- creatinine ratio greater than 300-350 mg/mmol indicates Nephrotic range Proteinuria. Renal ultrasound is used to assess renal size and morphology; and may need to be performed urgently if signs of renal vein thrombosis are present (such as flank pain, haematuria renal impairment), for example, Doppler examination of the renal veins. Dipstic testing result are expressed as follow:

<table>
<thead>
<tr>
<th>Trace</th>
<th>0 or 15 mg/dl</th>
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<tbody>
<tr>
<td>2+</td>
<td>100 mg/dl</td>
</tr>
<tr>
<td>3+</td>
<td>300mg/dl</td>
</tr>
<tr>
<td>4+</td>
<td>Greater than 2000mg/dl</td>
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REFERENCES


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