# Chapter 11

# NEPHROTIC SYNDROME

## DEFINITION

Clinical syndrome in which gross proteinuria, always selective but to variable degree is present with mirror image hypoproteinaemia, edema, ascites and hyperlipaemia is present. Hypertension, azotemia, hypocomplementaemia and excessive erythrocyturia is sometimes present.

## CLASSIFICATION

### A. Congenital Nephrotic Syndrome:

Group of diseases determined prior to birth usually familial but sometimes inherited which present with edema in early weeks of life.

### B. Idiopathic Nephrotic Syndrome:

Group of diseases whose origin is unknown and in which any of wide range of histologic changes may be present.

### C. Secondary Nephrotic Syndrome:

Group of diseases in which underlying primary condition is known:

1. Collagen nephrosis:
    i. Anaphylactoid purpura.
    ii. SLE.
    iii. PAN.
2. Quartan malaria nephrosis.
3. Post nephritic nephrosis.
4. Membranous nephropathy.
5. Membranoproliferative.
6. Renal venous thrombosis.
7. Toxic nephrosis:
    i. Drugs: Troxidon.
    ii. Metals: Lead and mercury.
    iii. Envenomation.

8. Allergic nephrosis:
   i. Bee stings.
   ii. Pollen inhalation.
   iii. Immunization.
9. Rare causes:
   i. Amyloidosis.
   ii. Sickle cell disease.
   iii. Diffuse sarcomatosis.

## CONGENITAL NEPHROTIC SYNDROME (Finnish type)

On electron microscopy fusion of foot processes is seen. Immature or avascular glomeruli are seen in cortex and at later stage proliferative glomerular destruction occurs. Interstitial cells contain monocytes and plasma cells and tubular dilatation of proximal tubules is seen. Mesangial cell proliferation may occur.

Presentation is with edema and gross proteinuria in first month of life. Placental weight is usually more than 25% of newborn's weight. Postural deformities of hands and feet together with wide cranial sutures are present. Mirror image hypoproteinaemia with hypogammaglobulinaemia are seen.

Death occurs due to fulminant bacterial infection within weeks or months of life.

Infant is grossly edematous. Ascites may cause herniation. They are hypotonic, lie in opisthotonus and are non responsive to steroids, cytotoxic and dietary treatment. Diuretics may palliate anasarca. Death occurs from renal insufficiency.

Detection of affected fetus in utero is possible by detecting excess alpha feto protein in amniotic fluid. Abortion is recommended if test proves positive.

With renal transplant after bilateral nephrectomy in neonate and after correction of renal loss of albumin and gamma globulin it is possible to maintain life by haemo or peritoneal dialysis. Renal transplant can be carried out within first year of life.

## IDIOPATHIC NEPHROTIC SYNDROME

Glomerular insult may be due to variety of immunologic insult to glomeruli. 80-90% of children with INS have minimal changes in histology.

Antigen antibody reaction to virus infection like herpes simplex acquired in infancy and early childhood remains latent and capable of being realighted throughout life. Demonstration of cell mediated immunity in INS is complementary evidence. Demonstration of IgE in glomeruli is reported. Cow milk antibodies are seen in significant proportion of children.

**Clinical Features:**

Relapses occur in winter clusters.

Maximum age incidence between 1-5 years. Peak around second birthday. Onset is insidious with periorbital edema. History of preceding respiratory infection is obtained in only one third of cases but such infection preceds high proportion of relapses. Such infection is usually coryzal in type.

Untreated, scrotum may become grossly distended and can rupture if skin becomes ulcerated.

Increased intra abdominal pressure everts umbilicus and displaces heart and liver upwards.

Gross periorbital edema obstructs vision, predisposes to infection and conjunctivitis and may cause grave eyes damage.

Pleural transudates are commonly present.

Complete shedding of edema may occur spontaneously or follow acute infections.

Polyuria of diuresis is accompanied by dilution of proteinuria and this may be mistaken for reduction of proteinuria. This type of diuresis after stress was rationale for deliberately giving measles or malaria to children with INS.

Spontaneous improvement is inevitable in considerable proportion. Spontaneous recovery can occur after many years of proteinuria and proteinuria can persist for years without obvious deterioration of renal functions.

**Complications:**

Increased tendency to thrombosis with changes in blood coagulation, fibrinolysis and blood chemistry. These include elevation in factor 5, factor 8, fibrinogen, plasminogen and alpha 2 macro globulin with antiplasmin activity and lowered alpha 1 anti trypsin.

Tubular dysfunction may occur in children with INS and include proximal and distal hyperchloraemic acidosis, renal glycosuria, hyperkaluria, hyperaminoaciduria and difficulty in homeostasis.

Urinary tract infection is common complication in INS.

INS is always disease in which majority of cases tend to recover completely, unless dying of acute infection or toxic complications of drug therapy.

**Diagnosis:**

1. Soft gravitational edema.
2. Selective proteinuria.
3. Hyperlipaemia.
4. Mirror image hypoproteinaemia.

**Differential Diagnosis:**

1. Congenital and secondary nephrotic syndrome.
2. Other causes of proteinuria.
3. Oligoalbuminic edema as in kwarshiorkor, coeliac disease.
4. Protein losing enteropathy.
5. Angioneurotic edema.
6. Nephritic syndrome.

**General Management:**

Child should be supervised from local center preferably within easy reach of home and where schooling can be preserved and coordinated between hospital and home.

Finance may be of importance and traveling cost, drug and hospital costs may be prohibitive to individual in developing country.

Psychological problems arise. Parents may feel it easier to accept steroids resistant case progressing towards death rather than intermittent ballooning of recurring edema in frequentely relapsing steroids sensitive child.

Steroids obesity and cyclophosphamide baldness are predictable and parents should be warned. They respect prescience which cement good doctor – parents – child relationship.

During period of gross edema and ascites patient is lethargic and content to rest in bed.

Grossly distended scrotum should be supported and foot of bed raised considerably to permit drainage.

Gross ascites causing respiratory distress may mandate paracentesis abdominis but it rarely required with effective diuresis and salt poor albumin availability.

When gross periorbital edema prohibits vision head should be elevated and eyelids will drain gravitationally. This will tend to increase edema of genitalia.

As edema lessens child should be allowed up and about.

Increased tendency to thromboembolism exists especially if dehydration occurs following diuresis specially for patients on steroids therapy.

When chronic renal failure arises it must be treated on standard lines.

## ROLE OF RENAL BIOPSY

Rarely of benefit to individual patients and difficult to justify for typical INS without azotemia, hypertension or erythrocyturia, particularly if there is highly selective proteinuria and normal C3 level.

Best test of steroids response is steroids therapy not biopsy.

Biopsy is best reserved for frequent relapser, children aged 8 years or more, atypical cases and in relation to scientific research. Children who do not respond to 6 weeks steroids therapy should be biopsied.

Biopsy result may help contraindicate long term intensive steroids therapy for small proportion of children with persistent hypocomplementaemia and membranoproliferative histology membranous histology or any other proliferative lesions.

## DIET

Water intake is restricted to 1000 ml daily. When gross diuresis is provoked water intake be increased promptly to avoid risk of thrombosis.

High protein low sodium diet is given until patient is free from edema or proteinuria or until uraemia ensues. Satisfactory diet is achieved by cooking all vegetables without salt, adding no salt at table and by reducing intake of milk. Diet should contain 75-100 gms of proteins daily. This helps to compensate for proteinuria, conserves tissue protein and lessens emaciation. When steroids are introduced calorie restraint reduces steroids obesity. Where specific protein sensitivity is suggested or antibodies to protein is shown diet free of specific protein is reported to produce amelioration.

Gross proteinuria and sodium retention may last for days, weeks or many years but eventually renal insufficiency and uraemia relentlessly begin. At this stage large intake of water is essential since child with isosthenuria is drinking to live. Protein content of diet should be reduced to 25 gms daily.

## ANTIMICROBIAL THERAPY

### A. Prophylactic Antibiotics:

Organism concerned are streptococci, pneumococci sensitive to penicillin. Antibiotics resistance and superinfection with resistant organisms may occur.

When patient on steroids therapy is exposed to infection by virus such as measles it is desirable to give gamma globulin to help mitigate likely severe attack of disease.

Specific immunoglobulins against zoster or varicella are useful adjuvant to treatment for children receiving immunosuppressant drugs and accidentally exposed.

### B. Therapeutic Antibiotics:

This depends upon sensitivity tests on organism. In majority organism is pneumococci and penicillin is highly effective. Low grade cellulitis is typical in these cases. Pneumococcal peritonitis is common. Rarely fulminant gram negative sepsis with death from bacterimic shock occurs. Intravenous cephalosporins are given in such cases.

Pyelonephritis occurs commonly in steroids resistant children with INS. It should be eradicated by antibiotics before beginning steroids or cytotoxic therapy.

Prophylactic cover should be maintained with cotrimoxazole and nitrofurantoin. When steroids resistance is noted always exclude urinary tract infection.

## DIURETIC THERAPY

Object of diuretic therapy is to increase output of sodium and water. Best diuretic treatment for most INS is response to steroid therapy.

For congenital, secondary or steroid resistant cases diuretics may be indicated as follows:

**A. Prior to Steroid Therapy:**

1. With gross anasarca when percutaneous biopsy is desired or patient distressed.
2. If susceptible patient has been in contact with chicken pox and measles.
3. If infection such as urinary tract infection is present.
4. If clinical, biochemical, haematological or histological data contraindicate steroid therapy.

**B. Following Steroid Therapy:**

1. When disease is resistant to steroids therapy.
2. When gross steroids effects have been produced such as hirsutism, obesity, hypertension, dwarfism and osteoporosis.
3. When steroids toxicity such as fits, diabetes or papilledema have been produced.

There are 3 groups of diuretics:

**A. Plasma Expanders:**

Salt poor albumin intravenous 0.5 gm per kg. Effect is transient because albuminuria increases and situation reverts back to hypoalbuminic state. Dangers are transmission of infection.

**B. Thiazide Diuretics:**

Chlorthiazide and hydrochlorthiazide which is 10 times more potent. They cause tubular loss of potassium.

Chlorthiazide is given 250 mg 6 hourly. Hydrochlorthiazide 25 mg 6 hourly.

Benzothiadiazines produce diuresis by interfering with tubular reabsorption of sodium ions. Gastrointestinal symptoms, skin eruptions and thrombocytopenia occurs. Hyperglycaemia and hyperuricaemia may occur.

**C. Frusemide:**

Natriuretic effect when given orally is complete in 4 hours. After intravenous injection diuresis begins in 1-2 minutes and completed in 2 hours. Drug is partly metabolized in vivo and is largely eliminated by combination of tubular secretion

and glomerular filtration. There is consistent change in glomerular filtration rate after frusemide. Oral dose 20-80 mg. Intravenous 10-40 mg. Intravenous dose useful in pulmonary edema and cerebral edema. This may be combined with intravenous albumin in resistant nephrotic edema or with spironolactone or triamterene therapy.

**D. Spironolactone:**

Aldosteron antagonist reducing sodium reabsorption from distal renal tubule. It has structure similar to aldosteron and acts as antagonist at target site.

With low sodium intake spironolactone leads to natriuresis with potassium conservation. Dose 25 mg 6 hourly orally. Drug is used as complementary to thiazide or frusemide which ensure that adequate quantity of sodium is presented to distal tubule. In presence of aldosteron antagonism exchange of sodium for potassium or hydrogen ions is reduced and consequently excretion of sodium takes place.

Combination of thiazide with spironolactone can be continued indefinitely in symptomatic treatment of edema.

**Complications of Diuretic Therapy:**

Hyperkaluria and hypokalaemia should be anticipated and prevented. Clinical signs of fatigue and weakness are not reliable. ECG monitoring is useful. Supplemental potassium 25 mmol daily should be given.

## CORTICOSTEROID THERAPY

There are two types of treatment:

**1.** Continuous high dose with tapering dosage at end.

Schedule of oral prednisolone:

1. Day 1-10: 60 mg daily.
2. 11-20: 40 mg daily.
3. 21-30: 20 mg daily.
4. 31-40: 10 mg daily.

ACTH may be injected intramuscular on 3 occasions during last 10 days of prednisolon treatment to reawaken adrenal glucocorticogenesis although this will not awake pituitary activity.

**Contraindications to Steroids:**

1. Persistent hypocomplementaemia. (Biopsy advised to exclude membranoproliferative histology).
2. Haematuria, systemic hypertension, azotaemia (biopsy advised)
3. Exposure to measles or varicella.
4. Bacterial infections eg pyelonephritis. (Both above are temporary contraindications).

5. Peptic ulcer.
6. Lack of adequate supervision.

95% cases respond within 8 weeks. 35-40% cases do not relapse.

Steroid dose is not by weight because edema negates accurate use of height: weight nomograms.

**2.** Intermittent corticosteroid therapy every 48 hours or 3 days in every 7. Initial corticosteroid therapy will divide patients into those who respond and those who do not.

Response is defined as less than 100 mg proteinuria per day. Transient return of slight proteinuria at end of intensive steroids therapy may occur. Transient proteinuria may occur later when upper respiratory infection has occurred intercurrently. Such proteinuria is not indication for restarting steroids and patient should be left for 2-3 weeks during which period proteinuria will disappear. When proteinuria persists for 2-3 weeks or if edema recurrs then second fully tapered course of prednisolone is given to deal with underlying immunologic upset.

Patient who relapses and responds completely to retreatment with prednisolon does not require biopsy. Such children are almost always minimal change.

If relapse occurs during intermittent therapy or two relapses within 6 months of onset then patient is likely to become frequent relapser and possibility of cyclophosphamide therapy should be considered.

Child who is non responsive to prednisolon and does not have urinary tract infection should be subjected to biopsy. Many will be minimal change and will recover within one year either with or without steroids therapy if effective diuretic, dietetic and antimicrobial cover is given.

Dangers of steroids therapy:

1. General:
   i. Cushingoid obesity with buffalo hump.
   ii. Increased appetite.
   iii. Altered physiological and mental state.
   iv. Euphoria.
2. Cutaneous manifestations:
   i. Poor wound healing.
   ii. Cutaneous striae which may lead to spontaneous weeping of skin.
   iii. Hirsutism of trunk, face, pubic and moustache area.
3. Gastrointestinal:
   i. Abdominal distension simulating obstruction due to faecal impaction.
   ii. Peptic ulcer.
   iii. Pancreatitis.
   iv. Hepatomegaly.

4. Diabetes mellitus.
5. Immunological:
    i. Decreased resistance to infection and flaring of latent tuberculosis.
6. Skeletal:
    i. Delayed growth.
    ii. Osteoporosis.
    iii. Compression fracture.
    iv. Reduced bicortical/transverse bone ratio (osteoporotic index).
7. Cardiovascular:
    i. Systemic hypertension.
    ii. Acute left ventricular failure.
    iii. Thromboembolism.
8. Haematological:
    i. Leucocytosis.
    ii. Thrombocytopenia.
9. Neurological:
    i. Convulsions due to hypertension and hypokalaemia.
    ii. Papillaedema.
    iii. Pseudotumor cerebri.
10. Cataracts.

Growth retardation is followed by period of catch up growth but catch up may not occur if therapy is prolonged for more than one year. Mechanism involves somatomedin and blockade of RNA synthesis.

Biocortical thickness is expressed as percentage of total transverse diameter of 3 bones such as metacarpal, femur and spinal body.

## CYTOTOXIC THERAPY

Cyclophosphamide is effective in treatment of steroids sensitive patients who relapse frequently. Proteinuria should first be abolished by corticosteroid therapy and when diuresis ensures free flow of urine then cyclophosphamide is started whilst patient continues to receive 10-20 mg prednisolon daily. Cyclophosphamide is given in dose of 2.5-3 mg per kg per day orally with high fluid intake for 8 weeks. With concomitant corticosteroid therapy leucocyte count is rarely depressed below 4000/cu mm. If polymorphs fall below 1000/cu mm or total leucocyte count below 2500/cu mm stop therapy temporarily and resume when leucocyte count rises. Taper steroids after stopping cyclophosphamide and then stop steroids altogether.

Long remission occurs in most frequent relapsers and after 5 years or more 50% remain well. Period free of steroids therapy is beneficial to physique and growth of patient.

Cyclophosphamide is rarely effective in treatment of steroids resistant patients except late steroids responders with minimal change histology.

Severe toxic effects may occur. Partial and reversible baldness is common. Depression of resistance makes patients very vulnerable to virus infection especially measles and varicella, bacterial sepsis and moniliasis. Danger is more when cytotoxic therapy is combined with steroids.

Toxic effects are mutagenic, carcinogenic and sterilizing. Gross chromosomal changes can be produced. If such mutations occur and were to persist in gonadal clone they could prove frightening complication if cyclophosphamide is used in children who survive to reproduce. Sterility may be temporary or permanent and relative or absolute.

Guidelines for cyclophosphamide therapy:

1. Explain potential dangers to parents and take informed consent.
2. Use cyclophosphamide only for steroids toxic, steroids sensitive, frequently relapsing cases of idiopathic nephrotic syndrome.
3. Provoke diuresis with steroids therapy prior to giving cyclophosphamide therapy and ensure adequate urine flow round the clock and thus reduce risk of haemorrhagic cystitis.
4. Continue low dose steroids therapy (10-20 mg per day) during cyclophosphamide therapy to reduce risk of agranulocytosis.
5. Give 8 weeks treatment of cyclophosphamide in dose of 2.5 mg per kg per day orally.
6. Taper and stop steroids after cyclophosphamide therapy stops.
7. Protect child against virus infection.

## PROGNOSIS

With modern treatment and no cytotoxic drugs about 70% will be well, 20% will have proteinuria and other complications and 10% will be dead after 5 years.

Prognosis is worse in those patients who have membranous lesions, chronic hypocomplementaemia and membranoproliferative lesions or focal glomerulosclerosis.

Initial haematuria, azotaemia, systemic hypertension or onset after age 7 years are not encouraging.

Most ominous sign is no response to steroid therapy.

When previously steroids responsive relapsing patient subsequently does not respond to steroids, course of cytotoxic drugs produce longer remission in steroids sensitive relapsers.

Long term prognosis is good. Most children cease relapsing by early adulthood.

## SECONDARY NEPHROTIC SYNDROME

**A. Collagen Nephrosis:**

Anaphylactoid nephritis may have nephritic period. SLE and PAN also have nephrotic stage. Treatment is symptomatic.

**B. Quartan Malaria Nephrosis:**

Caused by P. Malariae. Peak age incidence is 8 years. Presentation is with classical features of nephrotic syndrome ie hypoproteinaemia, gross proteinuria, edema and ascites. Concomitant infestation with tape worm and round worm may be present. In idiopathic nephrotic syndrome proteinuria is always highly selective. In malaria nephrosis it is not. In QMN level of plasma C3, IgA, IgG and IgM tend to be low. Therapeutic trial with steroids is given. If good response is obtained (as in 15% of Nigerian children then INS is likely cause. If no response or poor response is obtained then QMN is probable cause.

Biopsy in early stage reveal involvement of few glomeruli in segmental manner. At later stage segmental sclerosis appears in mesangium sometimes with epithelial crescent. Tubular atrophy follows. Immunofluroscent study shows deposits of IgM, IgG, C3 and plasmodium malariae antigen on glomerular basement membrane indicating this to be immune complex disease. Electron microscopy reveals thickened and duplicated basement membrane.

Clinical presentation varies with duration of disease. Hyperlipaemia and hypercholesterolaemia are less marked. Excessive erythrocyturia is more commonly present than in INS.

Prognosis is poor and is worse progressively as disease becomes longer established. Eradication of Plasmodium malariae infestation produces no amelioration. Most cases are resistant to steroids except in early stage.

Treatment with azathioprine and cyclophosphamide have been tried. Optimum approach is eradication of mosquitoes.

Schistosomiasis may have similar effect.

**C. Post Nephritic Nephrosis:**

Nephrotic syndrome is commoner following anaphylactoid nephritis. It is more usual to have mixed picture of nephritic and nephrotic syndrome which has poor prognosis.

Treatment is symptomatic. During period of edema dietetic, diuretic and antimicrobial therapy is required. In later stages hypertension and progressive renal insufficiency require treatment.

**D. Renal Vein Thrombosis:**

Nephrotic syndrome is rare in course of this disease in children. Treatment is of primary condition with symptomatic treatment of nephrotic state.

**E. Toxic Nephrosis:**

Basic approach is to prevent it if possible by removing mercury and prevention of snake bite. Recovery occurs on removal of offending agent.

**F. Allergic Nephrosis:**

Nephrosis following insect stings and immunization is unusual. When reaction occurs to immunization procedure which mandates subsequent reinoculation possibility of renal complications must be remembered. Children with INS in remission should not be allowed to have subsequent immunization.

In pollen nephrosis IgE deposits are seen in glomeruli. Similar deposits are seen in patients with focal glomerulosclerosis.

❑