

NEPHROTIC SYNDROME: MINIMAL CHANGE DISEASE

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Heavy Proteinuria. Edema. Hyperproteinemia. and Hyperlipidemia characterize the nephrotic syndrome (NS).

CLASSIFICATION

The syndrome can be divided into congenital, primary (idiopathic), and secondary types.

1. Minimal-change disease. (75%)
2. Mesangio- proliferative. (<5%)
3. Focal-segmental lesion. (10%)
4. Membranous nephropathy. (<5%)
5. Membrano proliferative glomerulonephritis. Type I, II and III (10%).

ETIOLOGY

90% of the children have some form of the idiopathic nephrotic syndrome. Minimal-change disease is found in approximately 75%. Where as in 10% of the children with Nephrosis, the nephrotic syndrome is largely mediated by some form of glomerulonephritis, membranous and Membrano-proliferative are most common. It is widely accepted that minimal change nephrotic syndrome (MCNS) is the most common cause of nephritis in children. Recent studies show that the incidence of Focal Segmental Glomerulosclerosis (FSGS) in children with idiopathic nephrotic syndrome has increased recently.²⁹

PATHOPHYSIOLOGY

The underlying pathogenetic abnormality in Nephrosis is proteinuria, which results from an increase in glomerular capillary wall permeability. The mechanism of this increase in permeability is unknown but may be related, at least in part, to loss of negatively charged glycoproteins with in the capillary wall (glomerular basement membrane due to cationic proteins produced because of immune system disturbances). The cause of steroid sensitive NS remains unknown, although the prevalence is higher in atopic families and some studies suggest an abnormality of "T" cell function⁵⁻⁷. The protein loss generally exceeds 2g/24 hrs ($>40\text{mg}/\text{m}^2/\text{hr}$)² and is composed primarily of albumin; the hyperproteinemia is fundamentally a "hypoalbuminemia". In general edema appears when the serum albumin level falls below 2.5g/dl (25g/l)³

Edema is initiated by the development of hypoalbuminemia. the result of urinary protein loss. The hypo albuminuria leads to a decrease in the plasma oncotic pressure, which permits transudation of fluid from the intravascular compartment to the interstitial space. The reduction in intravascular volume decreases renal perfusion pressure, activating the renin-angiotensin-aldosterone system, which stimulates distal tubular reabsorption of sodium. The reduced intravascular volume also stimulates the release of anti-diuretic hormone, which enhances the reabsorption of water in the collecting duct. Because of the decreased plasma oncotic pressure, the reabsorbed sodium and water are lost into the interstitial space, exacerbating the edema.

In the nephrotic state, almost all serum lipid (cholesterol, triglycerides) and lipoproteins levels are elevated. Two factors offer at least partial explanation:

1. The hyperproteinemia stimulates generalized protein synthesis in the liver, including the lipoproteins;
2. Lipid catabolism is diminished, owing to the reduced plasma levels of lipoprotein lipase, the major enzyme system that removes lipids from the plasma. lipid abnormalities may contribute to the abnormal renal hemodynamics.

Minimal change disease;

TERMINOLOGY;

1. Proteinuria: $>2\text{g}/24\text{hrs}$. ($>40\text{mg}/\text{m}^2/\text{hr}$)² ($>50\text{mg}/\text{kg}$ per day)²⁸.
2. Hyperproteinemia: $<2.5\text{g}/\text{dl}$. (25g/l)³
3. Urinary protein/creatinine ratio $>200\text{mg}/\text{mmol}$.
4. Remission: urinary protein excretion $<04\text{mg}/\text{hr}/\text{m}^2$. OR reagent strip (Albustix) = ++/or more for 03 consecutive days.
5. Relapse: urinary protein excretion $> 40\text{mg}/\text{hr}/\text{m}^2$. OR reagent strip = ++/or more for 03 consecutive days, having previously been in remission.
6. Frequent relapses: Two or more relapses within six months of initial response. OR 04 or more relapses within 12 months.
7. Steroid dependent: 02 consecutive relapses occurring during corticosteroid treatment. OR relapse occurring within 14 days of cessation of steroid treatment.
8. Steroid resistant: Failure to achieve response inspite of 04 weeks' prednisolone 60mg/m²/day.

CLINICAL FEATURES:

NS is more common in Asians with an annual reported incidence of 9-16 per 100,000 as compared to 2-4 per 100,000 new cases in UK¹⁻². It is more common in some families.

There is a male to female ratio in steroid sensitive NS of 2:1 with the condition starting between the ages of 2 to 6 years. There is often an antecedent history of viral upper respiratory tract infection that often precipitates the relapse. The children often present with peri-orbital edema usually confused with allergic conditions, and pitting edema in the lower extremities. The edema accumulates in dependent sites and appears to shift from the face and back to the abdomen, perineum and legs as the day progresses.¹ The edema may become generalized with ascites, pleural effusion and diminishing urinary output. There may be lethargy, irritability, poor appetite, diarrhea, and abdominal pain, which can even lead to referral to surgical units. Transient hypertension may occur in 10-15% of cases. Hypovolemia may cause peripheral circulatory failure and predisposes to thrombosis.²

INVESTIGATIONS

To establish diagnosis:

1. Urine for albumin.
2. Serum proteins and A: G ratio.
3. Serum cholesterol.
4. 24 hrs urinary proteins.

To find the cause

1. Urinalysis (to rule out infection).
2. Blood *complete* picture and ESR.
3. Blood urea.
4. Serum creatinine.
5. C3 complement levels.
6. LE cells.
7. Anti-nuclear factor.
8. Renal biopsy. (Refer to the criteria for renal biopsy).

DIAGNOSIS

May be summarized as following:

1. Urinary proteins+3 or more.
2. 24 hrs urinary protein excretion >2gms.
3. Serum albumin levels usually less than 2.5g/dl.
4. Elevated serum cholesterol and triglyceride levels.
5. I Reduced total serum calcium levels.
6. Normal serum complement C3 levels.
7. Urinary podocytes may be a useful diagnostic indicator for differentiation between FGS and MCNS. These cells may also mark disease progression in cases of FGS.³²

TREATMENT

The first episode of NS can be managed as outpatient for diagnostic, educational, and therapeutic purposes. After the diagnosis is confirmed by various appropriate laboratory studies, pathophysiology and treatment must be discussed with the parents, to enhance the understanding of their children's disease. Adequate information and often-repeated explanation about the benign nature of the disease has to provide to the parents. It should be made clear that minimal change NS does not progress to end stage renal failure, but relapses are frequently encountered and it is unusual for the disease to be active beyond the puberty. Appropriate and simple language should be used. The expected side effects of the drugs, and the need for vaccination has to be explained.

PHYSICAL ACTIVITY

The child should be actively mobilized and bed rest avoided, may continue to attend the school and the physical activity as tolerated. Children with edematous genitalia may restrict the activity because of discomfort. Elevation of genitalia with pillows enhances resolution of edema under the effect of gravity.

DIET

When periorbital edema develops, sodium intake is restricted. "No added salt diet" is started till the edema resolves. The fluid intake restriction is not recommended until the edema is moderate to severe.

A balanced palatable diet, with proteins Ig/kg/24hrs is recommended.

Rapid loss particularly of proteins leads to hypovolemia, with septicemia, if it is associated with diarrhea or injudicious use of diuretics. Hypovolemic crisis is heralded by abdominal pain, diagnosis confirmed by hypotension, cold extremities, sluggish capillary flow, wide peripheral and central temperature difference, raised packed red cell volume and very low urinary sodium concentration (I-2mmol/l). A rapid infusion of plasma (PPF) 20ml kg is essential in such circumstances².

In some instances, 25% human albumin Ig/kg24hrs followed by furosemide may be necessary; but the effect is transient and volume over load with hypertension and heart failure must be avoided¹.

DIURETICS

If the edema becomes mild to moderate chlorothiazide. 10-40 mg/kg'24hr (in two divided doses) may be started, at home, if hypokalemia develops, an oral potassium chloride supplement or

spironolactone. 3-5 mg/kg/24 hr (in 3-4 divided doses) may be added.

In cases with severe edema (massive pleural effusion, ascites, scrotal edema) oral furosemide (1-2mg/kg every 4hrs) in conjunction with metolazone (0.2-0.4mg kg/24hr) may be initiated. For patient's resistant to oral diuretics, intravenous administration may be effective, intravenous furosemide. after a loading dose of 1mg/kg, should be given as a constant infusion at a rate of 1mg/kg/hr in combination with chlorothiazide 10mg/kg every 12 hrs.

A recent study conducted in India reported that enalapril is effective in reducing proteinuria and thereby the morbidity in steroid resistant nephrotic syndrome irrespective of the underlying pathology.³⁰ Another study showed that ACE inhibitor treatment significantly improved glomerular membrane size-selective dysfunction. This effect persisted more than 2 months after treatment withdrawal. No patient had symptomatic hypotension, acute renal function deterioration, or hyperkalemia during enalapril treatment. Thus, in-patients with IMN and long-term nephrotic syndrome, ACE inhibitor treatment, but not conventional therapy, improve glomerular barrier size selectivity. The antiproteinuric effect of ACE inhibition is long lasting, especially in-patients with more severe renal insufficiency.³³

CORTICOSTEROIDS

Children with the onset of NS between the ages of 1 and 8 years are likely to have steroid-responsive- minimal-change disease; corticosteroid treatment should be initiated without renal biopsy. Minimal change disease remains common in children who are older than 8 yrs and present with nephrosis; renal biopsy is recommended by some to establish a firm diagnosis before considering therapy in this age group.

At present a high dose of prednisolone (60mg/m²/day, max. 80mg/day) is accepted practice in most units in the UK. For induction of remission (urine negative or with trace amounts of proteins on reagent strips for three consecutive days). The steroid dosage can also be calculated on ideal body weight (equivalent dose is 2mg/kg/day). The consensus view was that this dose of prednisolone should be continued (max. 28 days) until remission, which would be expected in 80% of children with NS, with 92% of these having minimal change histology. 80% of those patients who respond will do so within 14 days, although a further 14 days is generally needed to restore plasma albumin concentration to normal.⁶

Recent findings suggest that 16-week prednisolone treatment for the initial episode of INS may delay occurrence of the first relapse, but may lead to significant side effects. Prolongation of initial therapy may be useful in developing countries where frequent infections often induce early relapses.³

Opinions differ on the timing of treatment in NS relapses as it has long been known that upto 25% spontaneously remit (about 3% /day).¹³ Treatment can usually be deferred for upto 5days, but children should not be allowed to become edematous. Intensification of relapse treatment has little effect on the subsequent relapse rate.⁶⁻¹⁴

The characteristic feature of steroid sensitive NS is the tendency to relapse. Recent data suggest rates of 76-97% and frequently relapsing rates of upto 50%¹⁰⁻¹¹. There are no predictors of the risk of subsequent relapse after the initial episode, but the number of relapses with in the first 6 months of presentation is highly predictive of the subsequent course. -

Relapses generally respond much better than the initial attack and this may be related to the pharmacokinetics of prednisolone and the severe hypoproteinemic state of many children at presentation.⁶

Children with frequently relapsing or steroid dependent course need individualized treatment and should be managed in conjunction with a pediatric nephrologist. Treatment should be for a minimum of three to six months as an alternate day single doses regimen rather than intermittently, although selective patients may benefit from long term daily treatment.¹⁵ Most school age children can tolerate 0.5-6mg/kg/body weight on alternate days and the preschool child upto 1 mg/kg body weight.

ALTERNATIVE TREATMENT

It should be considered in the following circumstances:

1. Relapses on prednisolone dosage >0.3mg/kg body Wt/alternate days plus one or more of the following; (a) unacceptable side effects of corticosteroid treatment; (b) high risk of toxicity - boys approaching puberty or diabetes; (c) unusually severe relapses; hypovolemia or thrombosis; and (d) inadequate facilities for follow up or concern about compliance
2. Relapse on prednisolone > 1mg/kg/body wt/alternate days.

FIG. 1 OUT COME OF THE PATIENTS WITH NEPHROTIC SYNDROME

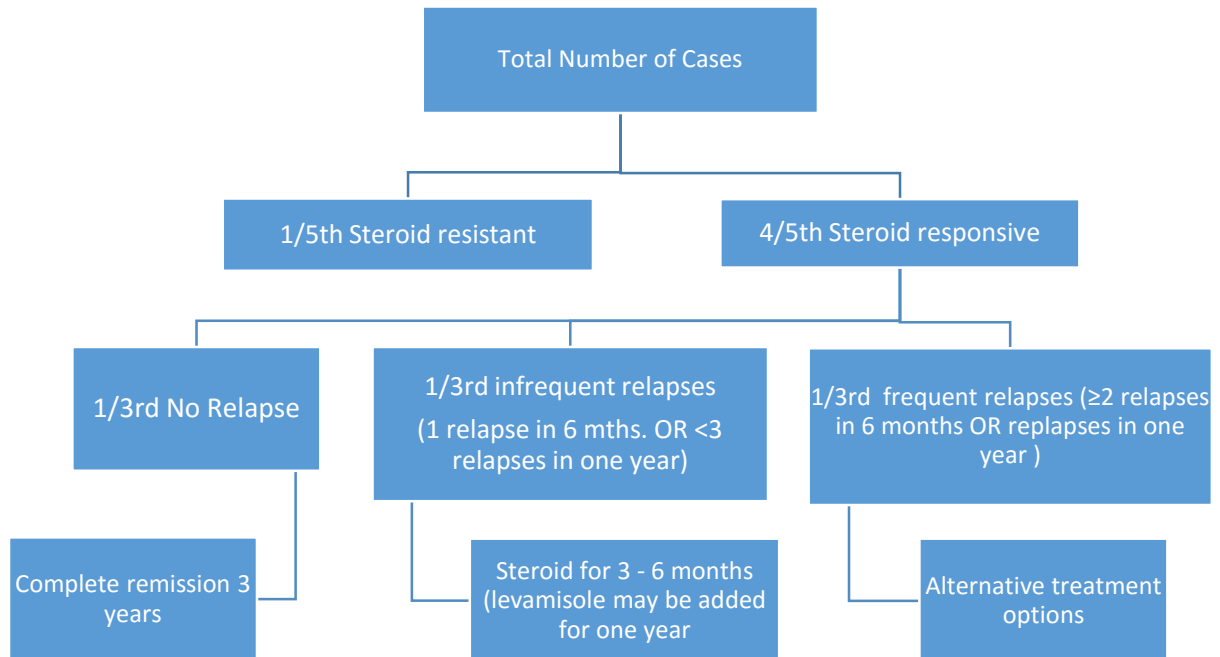


Table 1: Levels of management of steroid sensitive NS:

1. <i>Initial episode:</i> Prednisolone 60mg/m ² /day (max. 80mg/day) until remission, Followed by: Prednisolone 40mg/m ² /day (max. 60mg/day) on alternate days for 4 weeks.
2. <i>First two relapses:</i> Prednisolone 60mg/m ² /day (max. 80mg/day) until remission, Followed by: Prednisolone 40mg/m ² /day (max. 60mg/day) on alternate days for 4 weeks.
3. <i>Frequent relapses:</i> Maintain Prednisolone, 0.1-0.5mg/kg on alternate days in the morning, for 3-6 months, then reduce.
4. <i>Relapse on Prednisolone:</i> Increase the dose >0.5mg/kg/alternate days. Levamisole, 2.5mg/kg/alternate day for 4-12 months.
5. <i>Relapse on Prednisolone >0.5mg/kg/alternate days and/or steroid side effects/risk factors:</i> Cyclophosphamide 3mg/kg/day for 8 weeks OR Mechlorethamine (nitrogen mustard) 0.8mg/kg I/V in two courses of four daily injections, one month apart (27).
6. <i>Post Cyclophosphamide relapse:</i> As steps 2 and 3.
7. <i>Relapse on Prednisolone >0.5 mg/kg/ alternate day,</i> Cyclosporine 5mg/kg/day for one year.
8. <i>Post cyclosporine relapse:</i> Vincristine, cyclophosphamide and prednisolone combination. (24) OR pulse methyl prednisolone, Oral prednisone and cyclophosphamide. (25,26).
9. Immunoglobulin therapy is an alternative in the management of nephrotic symptoms in cases with chronic renal failure where an immunosuppressive treatment is irrelevant. (31)

OTHER THERAPEUTIC OPTIONS

There are three effective drugs in addition to corticosteroids in NS:

1. Alkylating agents: cyclophosphamide and chlorambucil have a powerful long lasting effect that has been clearly shown in controlled trials.¹⁹⁻²⁰
2. Levamisole, which has a weak steroid sparing effect.²¹
3. Cyclosporine, which has a suppressive effect attested by many reports.²² but which has only recently been confirmed by controlled trials.²³
4. A recent study conducted in India reported that enalapril is effective in reducing proteinuria and thereby the morbidity in steroid resistant nephrotic syndrome irrespective of the underlying pathology.³⁰

CRITERIA FOR PATHOLOGY OTHER THAN MINIMAL CHANGE (NS) AND RENAL BIOPSY

Minimal change disease does not require renal biopsy, which can be diagnosed by history and preliminary investigations. The pointers for lesion other than nephrotic syndrome and for the renal biopsy are:

BEFORE TREATMENT

Recommended:

1. Onset at less than 6 months of age (congenital nephrotic syndromes) and more than 11 yrs.
2. Initial macroscopic haematuria (in the absence of infection) at any age.
3. Persistent microscopic hematuria.
4. Hypertension and /or low plasma C3, especially if female and/or adolescent.

Discretionary:

1. Onset between 6 and 12 months of age.
2. Persistent hypertension, microscopic hematuria, or low plasma C3 levels.
3. Renal failure - persist cm. and not attributable to hypovolemia.

AFTER TREATMENT

Steroid resistance:

Persistence of hematuria, after 4 weeks of full treatment.

COMPLICATIONS

A recent review of several large series of children given steroids for a variety of renal diseases, revealed a treatment related mortality of 5%.²⁷

The mortality rate for NS is 1-4%, the main complications being infection and thrombosis.²⁹

Improved surveillance and more aggressive management should reduce this figure.

INFECTION

S.Pneumoniae is an important cause of infection in many centers routinely use polyvalent pneumococcal vaccine but pneumococcal sepsis and peritonitis have been reported in immunized children.^{16,30}

Chicken pox and measles remain the major viral threats to the immuno-suppressed child.

The varicella zoster immunity status could be checked as part of the routine evaluation, and many children are vulnerable. If there is exposure while taking high dose prednisolone or alkylating agents, zoster immunoglobulins should be given after discussion with the local virology laboratory. Acyclovir should be given as early as possible if the condition develops. Measles exposure necessitates checking of immunization status with quarantine measures and gamma globulin treatment for those at risk.

Children taking prednisolone for longer than one week, live vaccine should be avoided until the patient has been off daily steroids for three months. Live vaccines can be given if the child is on a low dose alternate day corticosteroid regimen. Killed vaccines are best given when the child is in remission. Live oral polio vaccine should not be given to siblings or close household contacts of children on a high dose (60mg/m²) prednisolone. Live vaccine should not be given concurrently with alkylating agents.

THROMBOSIS

Nephrotic patients are in a hypercoagulable state with high concentrations of fibrinogen, factor VIII: R Ag and a₂- macroglobulin with a reduction in both functional and immunological antithrombin III. There is thus a tendency to arterial and venous thrombosis. Aggressive investigation and treatment may be needed to prevent fatal episodes such as pulmonary thrombo embolism.

HYPERTENSION

In those children who respond to steroids in the short term only dietary advice is required. Patient with persistent nephrotic states may need drug treatment, but the issue is not resolved.

ACUTE RENAL FAILURE

Acute renal failure occasionally occurs in steroid sensitive NS, Oliguria with raised urea and creatinine concentrations suggest hypovolemia and the need for albumin infusions. Interstitial nephritis due to drug hypersensitivity should be considered and referral to a pediatric nephrology center is appropriate.

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