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Nephrotic Syndrome

● Nephrotic syndrome, a manifestation of glomerular disease, is characterized by **nephrotic range proteinuria & the triad of clinical findings associated with large urinary loss of protein: hypoalbuminemia, edema & hyperlipidemia.**
It is primarily a pediatric disease & is it 15 times more common in children than adult.
● **Nephrotic range proteinuria is defined as protein excretion of > 40 mg / m^2 / hr or a first morning protein : creatinine ratio of > 2-3:1.**
● The annual incidence is **2-3 cases per 100,000** children per year in most western countries & higher in underdeveloped countries resulting predominantly from malaria.

Etiology

● Most children with nephrotic syndrome have a form of **primary** or idiopathic nephrotic syndrome (INS).
● Nephrotic syndrome may also be **secondary** to systemic diseases.
● A number of **hereditary** proteinuria syndromes are caused by mutations in genes that encode critical protein components of the glomerular filtration apparatus.

Pathophysiology

● The underlying abnormality is an **increased permeability of the glomerular capillary** wall which leads to massive proteinurea & hypoalbuminemia. On biopsy, the extensive effacement of podocytes foot processes (the hallmark of idiopathic nephrotic syndrome) suggests a pivotal role for the podocyte.
● INS is associated with **complex disturbances in the immune system**, especially T cell-mediated immunity.
● In FSGS, a plasma factor, probably produced by a subset of activated lymphocytes may be responsible for the increase in capillary wall permeability. Mutations in podocyte proteins or genes are associated with FSGS.
● Steroid-resistant nephrotic syndrome can be associated with mutations in some genes of the glomerular filtration apparatus.
● Although the mechanism of edema formation in nephrotic syndrome is **incompletely understood,** it seems likely that in most instances, **massive urinary protein loss** leads to **hypoalbuminemia**, which causes a **decrease in plasma oncotic pressure & transudation of fluid from the intravascular compartment to the interstitial space**. The reduction in intravascular volume **decreases renal perfusion pressure, activating the rennin-angiotension-aldosterone system, which stimulates tubular reabsorbtion of sodium.** The reduced intravascular volume also stimulates the **release of antidiuretic hormone**, which enhances the reabsorption of water in the collecting duct. The reabsorbed fluid will shift from intravascular space to interstitial space (due to decreased plasma oncotic pressure) & causes increasing edema.

The previous theory does not apply to all patients with nephrotic syndrome because some patients have increased intravascular volume & decreased plasma levels of rennin & aldosterone. Therefore, other factors, including primary renal avidity for sodium & water may contribute to the formation of edema.

● In nephrotic states , **serum lipid levels (cholesterol & triglycerides) are elevated** due to:

1.Hyoalbuminemia stimulates generalized hepatic protein synthesis, including synthesis of lipoprotein. This is also why a number of coagulation factors are increased, increasing the risk of thrombosis.

2.Lipid catabolism is diminished as a result of reduced plasma levels of lipoprotein lipase related to increased urinary losses of this enzyme.

● There is an **increased risk of infections** (sepsis, peritonitis, pyelonephritis), especially with encapsulated organism such as Streptococcus pneumonia & Hemophilus influenza. Causes include:

1.Urinary losses of immunoglobulins & properdin factor B. 2.defective cell-mediated immunity 3.Immunosuppressive therapy 4.Malnutrition 5.edema or ascites acting as a potential culture medium.

● Nephrotic syndrome is a **hypercoagulable state** resulting from multiple factors: 1.vascular stasis 2.an increase in hepatic production of fibrinogen & other clotting factors 3.decreased serum levels of anticoagulation factors 4.increased plasma platelet production (as an acute phase reactant) & 5.increased platelet aggregation

The coagulopathy manifests with thromboembolic events.

Idiopathic Nephrotic Syndrome (INS)

● Approximately **90%** of children with nephrotic syndrome have INS.

● INS is associated with **primary glomerular disease without evidence of specific systemic cause.**

● INS includes multiple histologic types:

1. Minimal change nephrotic syndrome (MCNS): represents about **85%** of cases of nephrotic syndrome. The glomeruli appear normal or show a minimal increase in mesangeal cells & matrix. Findings on immunofluorescence microscopy are typically negative & electron microscopy simply reveals effacement of the epithelial cell foot processes. **More than 95% of children with MCNS respond to corticosteroid therapy.**

2. Mesangeal proliferation: approximately **50%** of patients respond to corticosteroid therapy.

3. Focal segmental glomerulosclerosis (FSGS): only **20%** of patients with FSGS responds to corticosteroid therapy. FSGS is often progressive, ultimately involving all glomeruli & **ultimately leads to end-stage renal disease in most patients.**

4. Membranous nephropathy.

5. Membranoproliferative glomerulonephritis.

Clinical presentations

● INS is more common in **males** (male to female ratio is 2:1) & most common between **2-6 years**, but it may present as early as 6 months of age until adulthood.
● MCNS is present in 85-90% of patients <6 yr of age & only 20-30% of adolescents in which FSGS represent the more common cause.
● The incidence of FSGS may be increasing & it may be more common in African-American, Hispanic & Asian patients.
● The initial episode & the subsequent relapses **may follow minor infections** & occasionally a reaction to insect bites, bee sting or poison ivy.
● Patient usually present with mild edema which is initially noted around the eyes & in the lower extremities.
● Nephrotic syndrome may initially be misdiagnosed as an allergic reaction because of the periorbital swelling that decreases throughout the day.
● With time, the edema becomes generalized with the development of ascites, pleural effusion, & genital edema.
● Anorexia, irritability, abdominal pain, & diarrhea are common.
● **Hypertension & hematuria are uncommon.**

Differential diagnosis

● **Causes of marked edema may include :**
1) Protein-losing enteropathy 2) Hepatic failure 3) Congestive heart failure 4) Acute or chronic glomerulonephritis. 4) Protein malnutrition.
● A diagnosis other than MCNS should be considered in children < 1 yr of age, a positive family history of nephrotic syndrome, presence of extrarenal findings (e.g. arthritis, rash, anemia), hypertension or pulmonary edema, acute or chronic renal insufficiency & gross hematurea.

Diagnosis

● **GUE:** 3+ to 4+ proteinurea.
● **Urinary protein excretion** > 40 mg / m^2 / hr.
● **Spot urinary protein : creatinine ratio** > 2.
● **Serum creatinine is usually normal**, but may be abnormally elevated if there is diminished renal perfusion from contraction of the intravascular volume.
● **Serum albumin** < 2.5 g / dl.
● **Serum cholesterol & serum triglycerides** are elevated.
● **Serum complement** levels are normal.
● **Microscopic hematuria in 20% of cases**.
● **Renal biopsy is not routinely performed if the patient fits the standard clinical picture of MCNS.** Children with features that makes MCNS less likely **(gross hematurea, hypertension, renal insufficiciency, hypocomplementemia, & if age of onset < 1 yr or > 8 yr) should be considered for renal biopsy before treatment.**

Treatment

*Steroid therapy

● Children with onset of uncomplicated nephrotic syndrome between 1 & 8 yr of age are likely to have steroid-responsive MCNS & steroid therapy may be initiated without a diagnostic renal biopsy:

● **Initial attack**: **Prednisone 60 mg / m^2 /day (maximum dose is 80 mg) given in a single daily doses for 4-6 consecutive weeks** (after confirming a negative PPD test & administering the polyvalent pneumococcal vaccine). More than 95% of children will respond to steroid therapy (clinical remission, diuresis, & urine trace or negative for protein for 3 consecutive days).

● After the initial course, the prednisone dose should be tapered to 40 mg / m^2 / day given every other day as a single daily dose for at least 4 wk, with slow tapering & discontinuation over the next 1-2 months.

● **Relapse**: many children with nephrotic syndrome experience at least 1 relapse **(3-4+ proteinuria plus edema).** Although relapse rate of 60-80% have been noted in the past, the relapse rate in children treated with longer initial steroid courses may be as low as 30-40%.

●**Relapse should be treated with Prednisone 60 mg /m^2 /day (maximum dose is 80 mg) in a single morning dose until the child enter remission.** The prednisone dose is then changed to alternate-day dosing as noted with initial therapy, & gradually tapered over 1-2 months.

*** Diuretics therapy**

● *Mild-moderate edema* :

● Low sodium diet until remission.

● Although there are no data to support their safety or efficacy, oral diuretics are used by many clinicians to control edema in children with nephrotic syndrome. Because of the increased risks of the thromboembolc complications, **diuretic use should be reserved for patients with severe symptoms & must be closely monitored.**

● *Severe symptomatic edema* (as large pleural effusion, ascites, or severe genital edema) :

● The child should be hospitalized.

● Sodium restriction.

●Fluid restriction may be necessary if the child is hyponatremic.

●A swollen scrotum may be elevated by pillows to enhance fluid removal by gravity.

● Diuresis may be augmented by the administration of loop diuretics **(furosemide),** orally or IV, although extreme caution should be exercised. Aggressive diuresis can lead to intravascular volume depletion & a significantly increased risk of intravascular thrombosis.

● When a patient has significant generalized edema with evidence of intravascular volume depletion (e.g. in hemoconcentration), **IV administration of 25% albumin (0.5-1 gm albumin / kg), as a slow infusion followed by furosemide (1-2 mg/kg/dose IV) is sometimes necessary.** Such therapy should be used only in collaboration with a pediatric nephrologists & mandates close monitoring of volume status, blood pressure, serum electrolyte balance, & renal functions. Symptomatic volume overload with hypertension, heart failure & pulmonary

edema is a potential complication of paranteral albumin therapy, particularly when administered as rapid infusions.

● Children with nephrotic syndrome should attend school & participate in physical activities as tolerated.

■ ***Steroid-resistant nephrotic syndrome*** **:** children who continue to have proteinuria (i.e. ≥ 2+ proteinuria) after 8 wk of steroid therapy. He is in need for diagnostic renal biopsy. It is usually caused by FSGS (80%), MCNS, or mesangeal proliferative glomerulonephritis.

■ ***Steroid-dependent nephrotic syndrome*** **:** relapse (3-4+ proteinuria plus edema) while on alternate-day therapy or within 28 day of completing a successful course of prednisone therapy.

■ ***Frequent relapsers*** **:** patients who respond well to prednisone therapy but relapse ≥ 4 times in 12-months period.

● Steroid-dependent patients, frequent relapsers & steroid-resistant patients are candidates for **alternative therapy**, particularly if the child has severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts &/or growth failure). The alternative therapy may include the following options:

1. Cyclophosphomide: 2 mg/kg/ day, as a single oral dose for 2-3 months with alternate day steroid therapy. S/E (neutropenia, disseminated varicella, hemorhhagic cystis, alopecia, sterility & increased risk of future malignancy. WBC count must be done weekly & the drug should be withheld if count<5000/mm3.

2.Cyclosporine or tacrolimus: S/E (hypertension, nephrotoxicity, hirsutism & gingival hyperplasia.

3. Mycophenolate

4. Levimazole: antihelminthic agent with immunomodulating effects.

● **Most patients who respond tocyclosporine, tacrolimus or mycophenolate therapy tend to relapse when the medication is discontinued. Angiotensin–converting enzyme inhibitors & angiotensin 2 blockers may be helpful as adjunct therapy** to reduce proteinurea in steroid-resistant patients.

● It has been suggested that **3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase-inhibiting drug** should be used to treat the hyperlipidemia seen in persistent nephrotic syndrome, but controlled data regarding risks or benefits are not available.

Other measures as:

● Pneumococcal vaccine (23-serotype +7-valent conjugate given in routine schedule), given in remission & off daily prednisone therapy. Vaccines can be administered after corticosteroid therapy has been discontinued for at least 1 month.

●Non-immune nephrotic children in relapse, if exposed to varicella, should receive **varicella-zoster immunoglobulin** (1 dose ≤96 hr after significant exposure)

● Influenza vaccine should be given yearly.

Complications

1. ***Infections*** **:** major complications of nephrotic syndrome.

■ **Spontaneous bacterial peritonitis** is the most frequent infection. There may be other infections like sepsis, pneumonia, cellulites, & UTI.

■ Streptococcal pneumonia is the most common organism causing peritonitis. There may be gram-negative bacteria like E. Coli.

- Because fever & physical findings may be minimal with steroid therapy, so high index of suspicion , prompt evaluation by culture of blood or peritoneal fluid, & early initiation of antibiotics are critical.

2. ***Increased risk of thromboembolic events*:**

- The incidence in children is **2-5%** which is much lower risk than that in adult.
- Thrombembolic events include renal vein thrombosis, pulmonary embolus, sagital sinus thrombosis, & thrombosis of indwelling arterial & venous catheters.
- Prophylactic anticoagulant therapy is not recommended in unless when there is previous thromboembolic event.
- **Aggressive diuresis should be avoided** & the use of indwelling catheters should be limited.

3. ***Hyperlipidemia*** particularly in complicated nephrotic syndrome, may be a risk factor for CVS diseases (**MI is a rare** complication in children).

Prognosis

● The majority of children with steroid-responsive nephrotic syndrome have repeated relapses which are generally decrease as child grows older.

● The patients who respond to steroid rapidly & who have no relapse during the 1st 6 months after diagnosis tend to have an infrequently relapsing course.

● *It is important to tell the family that :*

1. The child with steroid responsive nephrotic syndrome will not develop chronic renal failure.
2. The disease is rarely hereditary.
3. The child, in absence of prolonged cyclophosphomide therapy, will remain fertile.
4. To minimize the psychological effects of the condition & its therapy, children with INS should not be considered chronically-ill & should participate in all age-appropriate childhood activities & maintain an unrestricted diet when in remission.

● Children with steroid-resistant nephrotic syndrome (mostly due to FSGS) generally have a much poorer prognosis. These children develop progressive renal insufficiency, ultimately leading to end stage renal failure requiring dialysis or renal transplantation. Recurrent nephrotic syndrome occur in 30-50% of transplant recipients with FSGS.

Secondary Nephrotic Syndrome

It should be suspected in patients with **onset of disease > 8 yr, hypertension, hematuria, renal dysfunction, extrarenal symptoms (rash, arthralgia, fever) or hypocomplementemia.** Causes include:

1. ***Glomerular diseases*** as membranous nephropathy, membranoproliferative glomerulonephritis, postinfectious glomerulonephritis, lupus nephritis, & Henoch-Schnolien purpura nephritis.
2. ***Infections:*** in certain areas of the world, malaria & schistosomiasis are the leading causes of nephrotic syndrome. Other infections include hepatitis B &C, filaria leprosy, & HIV.
3. ***Malignancy*** especially in adult as carcinoma of lung & GIT, lymphoma especially Hodgkin type. Nephrotic syndrome can develop before or after malignancy is detected, resolve as tumor regresses, & return if the tumor recurs.
4. ***Drugs*** & chemicals as penicillamine, captopril, gold, NSAID, mercury compounds, ethosuximide, methimazole, chlorpropamide, trimethadione & phenytoin.

Congenital Nephrotic Syndrome

Congenital nephrotic syndrome is defined as **nephrotic syndrome manifesting at birth or within 3 mo of life.** A number of **structural & functional abnormalities of the glomerular filtration barrier** causing congenital nephrotic syndromes have been elucidated. It is classified as **primary** or as **secondary** to a number of etiologies such as in-utero infections (CMV, toxoplasmosis, syphilis, hepatitis B & C, HIV), infantile SLE or mercury exposure.

Primary congenital nephrotic syndrome is due to variety of inherited syndromes as **Finish** type congenital nephrotic syndrome, **Denyes-Drash** syndrome & **Pierson** syndrome.

Clinical presentations include severe generalized edema, poor growth & nutrition with hypoalbuminemia, increased susceptibility to infection, hypothyroidism (urinary loss of thyroxin-binding globulin) & increased risk of thrombotic events. Most infants have progressive renal insufficiency.

Treatment of secondary congenital nephrotic syndrome is by treatment of the **underlying causes** while that of primary congenital nephrotic syndrome includes **intensive supportive care** with IV albumin & diuretics, regular administration of IV gamma-globulin, & aggressive nutritional support (often paranteral), with attempting to **decrease urinary protein loss** with angiotensin-converting enzyme inhibitors, angiotensin 2 receptors inhibitors, prostaglandin synthesis inhibitors or even unilateral nephroctomy. If conservative management fails & patients suffer from persistent anasarca or repeated severe infections, **bilateral nephroctomies & chronic dialysis** is initiated. **Renal transplantation** is the definitive treatment of congenital nephrotic syndrome with reported recurrences even after transplantation.

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