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Nephrotic Syndrome

- Nephrotic syndrome (NS) is the clinical manifestation of glomerular disease associated with heavy (nephrotic-range) proteinuria (protein excretion of > 40 mg / m^2 / hr or a first morning protein : creatinine ratio > 2). The triad of clinical findings associated with NS arising from the large urinary losses of protein are: hypoalbuminemia (≤2.5 g/dL), edema & hyperlipidemia (cholesterol > 200 g/dL). It is primarily a pediatric disease & is it 15 times more common in children than adult.
- NS affects 1-3 cases per 100,000 children < 16 yr of age & without treatment is associated with a high risk of death mostly due to infection. 80% of children with NS respond to corticosteroid therapy.

Etiology

- Most children with NS have a form of primary or idiopathic nephrotic syndrome (INS).
- NS 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.

Pathogenesis

- The underlying abnormality in NS is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria & hypoalbuminemia.
- The podocyte which is a highly differentiated epithelial cell located on the outside of the glomerular capillary loop, plays a crucial role in the development of proteinuria & the progression of glomerulosclerosis.
- Podocyte injury or genetic mutation of gene producing podocyte proteins may cause nephrotic-range proteinuria. Immune or non-immune insults may affect podocyte function (viral infections, allergen, tumors, drugs).

Pathophysiology

- There are 2 opposing theories to explain edema in NS:

1. The underfill hypothesis: nephrotic-range proteinuria leads fall in plasma protein level & decrease in intravascular pressure. This leads to leakage of plasma water into the interstitium, generating edema & increased secretion of vasopressin & atrial natriuretic factor, which along with aldosterone, results in increased Na & water retention by the tubules. This hypothesis does not fit with some cases of NS with intravascular volume overload, not depletion, which may be explained by:
2. The overfill hypothesis: primary Na retention, with subsequent volume expansion & leakage of excess fluid into the interstutium.

- Hypelipidemia is thought to be the result of increased synthesis & decreased catabolism of lipid.
- Increased susceptibility to infection may be due to many factors, particularly hypoglobulinemia as a result of urinary loss of IgG & defect in complement system (urinary loss of complement factors especially C3 & C4 & alternative pathway factor B & D).
- Hypercoagulability is due to multiple factors: vascular stasis from hemoconcentration & intravascular volume depletion, increased platelets number & aggregibility & changes in coagulation factor levels.

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 NS. 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 respond 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.

Minimal change nephrotic syndrome (MCNS)

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-Americans.
- The initial episode & the subsequent relapses may follow minor infections & occasionally a reaction to insect bites, bee sting or poison ivy.
- Children usually present with mild edema which is initially noted around the eyes & in the lower extremities.
- NS may initially be misdiagnosed as an allergic reaction because of the peri-orbital 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.
- Absence of Hypertension & hematuria (nephritic features)

Differential diagnosis

- Causes of marked edema may include protein-losing enteropathy, hepatic failure, heart failure, acute or chronic glomerulonephritis & protein malnutrition.
- A diagnosis other than MCNS should be considered in children < 1 yr of age, a positive family history of NS, presence of extra-renal findings (e.g. arthritis, rash, anemia), hypertension or pulmonary edema, acute or chronic renal insufficiency & gross hematuria.

Diagnosis

- GUE: 3+ to 4+ proteinuria.
- Urinary protein excretion > 40 mg / m^2 / hr.
- first morning 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.
- Evaluation to rule out secondary NS (children ≥ 10 yr): complement C3 level, ANA, double-stranded DNA, Hepatitis B & C & HIV in high risk population & renal biopsy
- 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 hematuria, hypertension, renal insufficiency, hypocomplementemia, & if age of onset < 1 yr or > 12 yr) should be considered for renal biopsy before treatment.

Treatment

Treatment of the initial attack of MCNS

- Corticosteroids are the mainstay of therapy of MCNS. Children with onset of uncomplicated NS between 1 & 8 yr of age are likely to have steroid-responsive MCNS & steroid therapy may be initiated without a diagnostic renal biopsy. TB must be ruled out before treatment by negative purified purine derivative or interferon release assay.
- Prednisone or prednisolone 60 mg/m^2/day or 2 mg/kg/day (maximum dose is 60 mg) given in a single daily doses for 4-6 wk followed by alternate-day prednisone 60 mg/m^2 or 1.5 mg/kg as a single dose for 8 wk - 5 mo period with tapering the dose. 80-90% of children will respond to steroid therapy.
- Response is defined as the attainment of remission within the initial 4 wk of corticosteroid therapy.
- Remission consists of a urine protein:creatinine ratio of < 0.2 or < 1+ protein on urine dipstick testing for 3 consecutive days. Most children will respond within 2-3 wk of treatment.
- Relapse is an increase in the first morning urine protein:creatinine ratio > 0.2 or ≥ 2+ or for 3 consecutive days on albustix testing.
- Frequent relapses is ≥ 2 relapses within 6 mo after the initial therapy or 4 relapses in 1 yr period.

- Steroid dependent is a relapse during steroid tapering or a relapse within 2 wk of the discontinuation of therapy.
- Steroid resistance is the inability to induce remission within 8 wk of daily steroid therapy.

*** Management of the clinical sequelae of NS**

Edema

- In mild-moderate edema: low sodium diet until remission.
- In severe symptomatic edema (as large pleural effusion, ascites, or severe genital edema): The child should be hospitalized with Na restriction (< 1.5 g daily). Water/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 severe generalized edema with evidence of intravascular volume depletion (e.g. in hemoconcentration, hypotension, tachycardia), 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 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 parenteral albumin therapy, particularly when administered as rapid infusions.

Dyslipedemia

- Low fat diet (< 30% of calories with a saturated fat intake of < 10% calories with dietary cholesterol intake < 300 mg/day).
- There are insufficient data to use 3-OH-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor routinely in children.

Infections

- Children are at increased risk for infection with encapsulated bacteria especially pneumococcal disease. Spontaneous bacterial peritonitis presents with fever, abdominal pain & peritoneal signs (mostly due to *pneumococcus,* but Gram-negative bacteria may be the cause).
- Families should be counseled regarding the signs & symptoms of infections such as cellulitis, peritonitis & bacteremia. Children with fever or other signs of infection must be evaluated aggressively with appropriate culture & treated empirically with antibiotics.
- In spontaneous bacterial peritonitis, peritoneal fluid should be collected if there is sufficient fluid to perform a paracentesis & sent for cell count, Gram stain & culture. Peritoneal leukocyte count > 250 cells/µL are highly suggestive of spontaneous bacterial peritonitis.
- Antibiotics must cover *pneumococcus* & Gram-negative bacteria (as third generation cephalosporin).

Thromboembolism

- Imaging studies to confirm the presence of clot if needed. Anticoagulation therapy appears to be effective (as heparin, LMW heparin & warfarin).

Obesity & growth

- Corticosteroids therapy may increase BMI in overweight children (anticipatory dietary counseling is recommended). Growth may be affected with long-term steroid therapy (steroid-sparing strategies may improve linear growth).

Relapse

- Relapses are common especially in younger children, & are often triggered by URT or GIT infections. Treatment is similar to the initial episodes, except that daily prednisone is shortened. Daily high-dose prednisone is given until the child has achieved remission, & then switched to to alternate-day therapy with variable duration depending on the frequency of relapses of the child.
- Children are classified to infrequent or frequent relapsers & being steroid-dependent based on number of relapses in 1 year or their inability to remain in remission following discontinuation of steroid therapy.

Steroid resistance

- It is usually caused by FSGS (80%), MCNS or membranoploliferative glomerulonephritis. It requires further evaluation, including kidney biopsy, kidney function, urine protein excretion & urine dipstick test.
- It is associated with a 50% risk of end-stage kidney disease within 5 yr of diagnosis if patients do not achieve partial or complete remission (specifically FSGS).
- It is associated with poor patient-reported quality of life, hypertension, serious infections & thromboembolic events.

Alternative therapies to corticosteroids

- Steroid-dependent patients, frequent relapsers & steroid-resistant patients are candidates for alternative therapies particularly if the child has severe corticosteroid toxicity (cushingoid appearance, hypertension, cataracts &/or growth failure).

1. Cyclophosphomide: in frequently relapsing & steroid-dependent NS, 2 mg/kg/ day, as a single oral dose for 2-3 months with alternate day steroid therapy. S/E: neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility & increased risk of future malignancy. WBC count must be done weekly & the drug should be withheld if count<5000/mm3. The cumulative threshold dose above which oligospermia or azoospermia occurs in boys is > 250 mg/kg.
2. Calcineurin inhibitors (Cyclosporine or tacrolimus): in steroid-resistant NS, S/E (hypertension, nephrotoxicity, hirsutism & gingival hyperplasia.
3. Mycophenolate: in steroid-dependen or frequently relapsing NS.
4. Levimazole: antihelminthic agent with immunomodulating effects.
5. Rituximab: monoclonal antibody, in steroid-dependent &/or steroid-resistant NS.

- Most patients who respond to cyclosporine, 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 proteinuria in steroid-resistant patients.

Immunizations

- Give Pneumococcal vaccine (13-valent conjugant & 23-valent polysaccharide vaccines) & influenza vaccination annually to the child & household contacts.

- Defer vaccination with live vaccines until the prednisone dose is below either 1 mg/kg daily or 2 mg/kg on alternate days. Live virus vaccines are contraindicated in children receiving corticosteroid-sparing agents as cyclophosphamide or cyclosporine.
- Following close contact with varicella infection, give immunocompromised children taking immunosuppressive agents varicella-zoster immune globulin if available, immunize healthy household contacts with live vaccines to minimize the risk of transfer of infection to the immunosuppressed child, but avoid direct exposure of the child to gastrointestinal or respiratory secretions of vaccinated contacts for 3-6 wk after vaccination.

Prognosis

- Most children with steroid-responsive NS have repeated relapses which are generally decrease as child grows older.
- Children who respond rapidly to steroid & 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 NS is unlikely to develop chronic kidney disease.
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 NS (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 NS 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, extra-renal symptoms (rash, arthralgia, fever) or hypocomplementemia. Causes include:

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

Congenital Nephrotic Syndrome

- Congenital NS manifests at birth or within 3 mo of life. A number of structural & functional abnormalities of the glomerular filtration barrier causing congenital NS.
- 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 NS is due to variety of inherited syndromes as Finish type congenital NS, Denyes-Drash syndrome, Pierson syndrome & Galloway-Moat 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 NS is by treatment of the underlying causes while that of primary congenital NS 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 NS with reported recurrences even after transplantation.

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