**Nephrotic Syndrome in Pediatric Patients**

**Epidemiology**
- In the United States, incidence of 2.7 cases per 100,000 children per year
- Cumulative prevalence of 16 per 100,000 children
- More common in boys than girls in younger age groups, but once adolescence is reached there is no significant difference between genders
- Most commonly seen at ages 3 to 5
- Increased incidence and more severe disease seen in African American and Hispanic populations

**Pathophysiology**
- Normally, the glomerular filtration barrier is composed of 3 layers, listed from capillary side to Bowman’s space side:
  - Fenestrated endothelium
  - Glomerular basement membrane
    - Negatively charged to prevent the passage of large anionic molecules (such as albumin)
  - Visceral glomerular epithelium, also known as podocytes
    - Podocytes contain foot processes, which create a barrier
    - Small pores between adjacent foot processes are bridged by slit diaphragms
    - Podocytes affect the structure and function of both the glomerular basement membrane and the endothelial cells
- Size discrimination is accomplished by the pores in the glomerular basement membrane and podocytes which have a radius of approximately 40 to 45 angstroms

- In nephrotic syndrome, the normal glomerular filtration process is interrupted, resulting in protein passing through the filtration barrier and severe-range proteinuria
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- Commonly a defect in the podocytes and/or glomerular basement membrane
- Recent experiments have implicated T-Cells in the damage to podocytes leading to 2 common types of nephrotic syndrome (minimal change disease and focal-segmental glomerulosclerosis)
- Exact pathology varies depending on the specific type of nephritic syndrome

Types of nephrotic syndrome:
- **Minimal change disease**
  - Most common pathology found in childhood nephrotic syndrome (77-85% of cases)
  - Usually idiopathic, though an association with Hodgkin lymphoma has been studied in adult cases
  - As name implies, light microscopy of renal biopsy samples shows no change
  - On electron microscopy, effacement of the foot processes can be seen
  - Immunofluorescent staining for immune complexes is negative

- **Focal segmental glomerulosclerosis**
  - Accounts for 10-15% of cases
  - More common in adults
  - Light microscopy of renal biopsy sample shows scarring, or sclerosis, of portions of selected glomeruli which can progress into global glomerular sclerosis and tubular atrophy
  - Like minimal change disease, will see effacement of foot processes on EM and in most cases, negative

Foot process effacement seen in minimal change disease
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immunofluorescence (no immune complex or antibody deposition)

- Also usually idiopathic but can be associated with HIV or sickle cell disease
- Potentially on a spectrum with minimal change disease as opposed to being completely separate entities
  - The two share pathologic findings and occasionally respond similarly to treatment

Typical H&E stain of FSGS

- Membranoproliferative glomerulonephritis
  - More commonly presents as nephritic syndrome
  - Involves immune complex deposition
    - Granular pattern seen on immunofluorescence staining
  - On light microscopy, can see thickened basement membrane
- Membranous glomerulonephritis
  - Accounts for just 2-4% of cases in children, but the most common type in adults
  - Like membranoproliferative disease, can see thickened basement membrane and granular pattern on immunofluorescence
    - On electron microscopy, characteristic “spike and dome” appearance seen, with membrane deposition growing around subepithelial immune complex deposition
  - Can be a primary disease, or due to several other causes

Classifications:

- Primary nephrotic syndrome
  - Not due to any identifiable systemic disease
Secondary nephrotic syndrome
  o Caused by identifiable systemic disease
    ▪ Infections
      • Hepatitis B and C, HIV, malaria, syphilis
    ▪ Drugs
      • Non-steroidal anti-inflammatory drugs, heroin, lithium
    ▪ Malignancies
      • Lymphoma, leukemia
    ▪ Auto-immune
      • SLE
    ▪ Endocrine
      • Diabetes mellitus
Congenital nephrotic syndrome
  o Finnish type (CNF)
    ▪ Most common congenital nephrotic syndrome, with an incidence of 1 per 8,200 in Finland
      • Not only seen in Finland, it is especially prominent in Mennonites in Pennsylvania
    ▪ Genetic mutation in the NPHS1 gene which codes for the protein nephrin or NPHS2, which codes for the protein podocin
    ▪ Massive proteinuria starts in fetal life, and prematurity usually complicates pregnancies
    ▪ Treatment is aimed at supporting the patient’s growth until a transplant is available
  o Other genetic mutations that lead to nephrotic syndrome lead to a FSGS type pathology and include the following genes: CD2AP, TRPC6, WT1, ACTIN4, tRNA(leu), COQ2

CLINICAL PRESENTATION
  • Characteristic findings:
    o Proteinuria
    o Hypoalbuminemia
      ▪ Secondary to proteinuria
    o Generalized edema
      ▪ Due to a decrease in plasma oncotic pressure which follows massive albumin urinary losses
      ▪ Begins in areas with low resistance, which can be seen in minimal change disease’s characteristic eyelid swelling, or “puffy eyes”
        • Can also lead to scrotal or vulvar edema
    o Hyperlipidemia
      ▪ Likely due to increased hepatic production of very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL),
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and low-density lipoprotein (LDL) in response to hypoproteinemia

• Diagnostic criteria (must see both)
  o Serum albumin below 3 g/dL
  o Urine protein excretion greater than 50 mg/kg per day
    ▪ Or, greater than 3.5g of protein in a 24-hr urine sample

WORK-UP

• In the absence of identifiable systemic disease, the vast majority of patients that meet diagnostic criteria for nephrotic syndrome have minimal change disease and will be treated accordingly
• Other diagnostic tests, mostly aimed at identifying pathologic processes other than minimal change disease, include:
  o Urinalysis
    ▪ Hematuria can occasionally be seen in FSGS but is usually a sign of nephritic syndrome
  o Protein to creatinine ration from first void of morning
    ▪ UPr/Cr greater than 3.0 is consistent with nephrotic syndrome
  o Serum studies including electrolytes, creatinine, BUN, lipid panel, albumin, and complement levels
    ▪ Also, ANA for patients over ten years old, and hepatitis b/c and HIV testing
  o Renal biopsy if strong suspicion of pathology other than minimal change disease
• When to biopsy
  o Patients that meet all of the following criteria can be treated empirically without renal biopsy (other patients could benefit from biopsy):
    ▪ Between ages of 1 and 10
    ▪ None of the following present: hypertension, gross hematuria, elevated creatinine
    ▪ Normal complement levels

TREATMENT

• Prednisone 2 mg/kg per day for 4-6 weeks, followed by 1.5 mg/kg per day on alternating days for another 4-6 weeks
  o 95% of patients with MCD will go into remission following 8 weeks of corticosteroid treatment
    ▪ Remission defined as 3 consecutive days with no or trace protein on urinalysis
    ▪ Confirms diagnosis of MCD
  o Lower rates of remission seen in patients treated for 12 weeks instead of 8
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• If recurrent relapses despite adequate steroid therapy, consider cyclophosphamide, 2 mg/kg per day, for 8-12 weeks
• Cyclosporine can also be used instead of or following cyclophosphamide
• Loop diuretics, such as furosemide 2 mg/kg per day, can be used to treat fluid overload and edema
• Prophylactic penicillin can be used to prevent streptococcal or staphylococcal infection secondary to decreased complement levels
  o Pneumococcal vaccination should be given

COMPLICATIONS
• Acute renal failure
  o Usually reversible with restoration of intravascular volume
• Thrombosis
  o Secondary to urinary losses of antithrombin III and protein S
• Infection
  o Usually staphylococcal or streptococcal

PROGNOSIS
• For patients with minimal change pathology, prognosis is very good, with most patients going into remission following corticosteroid treatment
• For patients with focal-segmental glomerulosclerosis, prognosis is grave
  o Generally will progress to end-stage renal disease requiring dialysis and kidney transplant

References


4. UpToDate: Etiology, clinical manifestations, and diagnosis of nephrotic syndrome in children