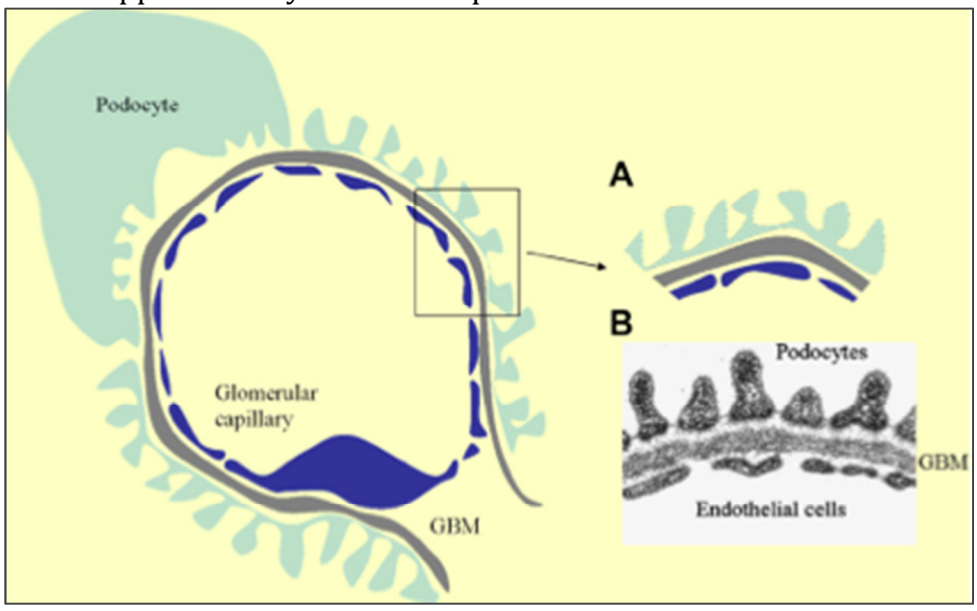
EPIDEMIOLOGY

- 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 amperes

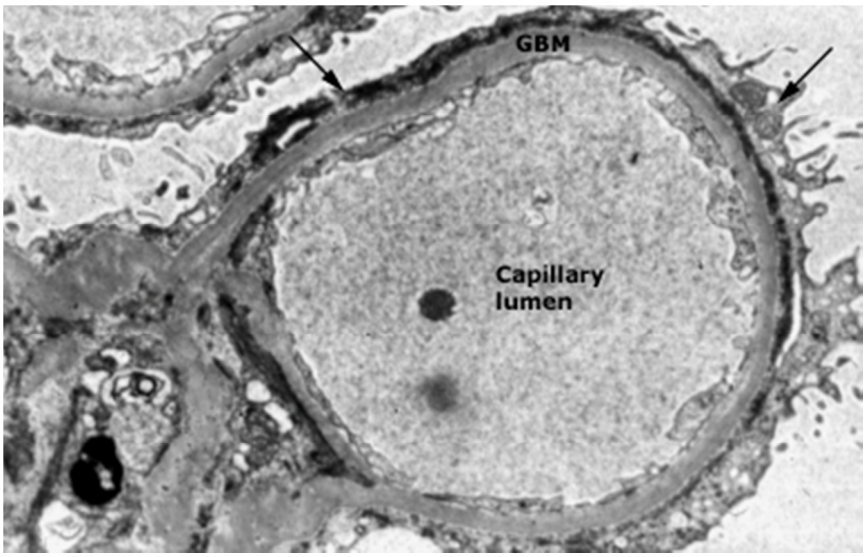


- In nephrotic syndrome, the normal glomerular filtration process in interrupted, resulting in protein passing through the filtration barrier and severe-range proteinuria

- 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:

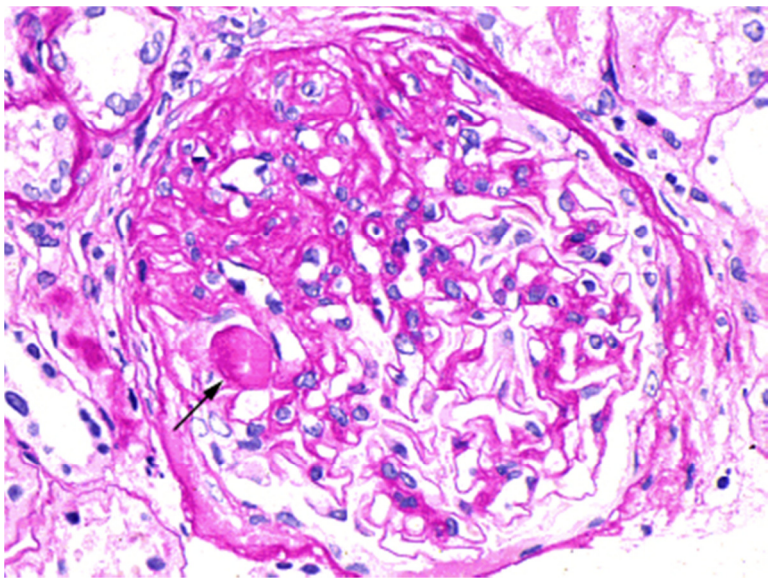
- Minimal change disease
  - Most common pathology found in childhood nephrotic syndrome (77-85% of cases)
  - Usually idiopathic, though an association with Hodgkin lymphoma has been studied in adult cases
  - As name implies, light microscopy of renal biopsy samples shows no change
  - On electron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



Foot process effacement seen in minimal change disease

- 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

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
    - 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
    - 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
    - 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:
    - Proteinuria
    - Hypoalbuminemia
        - Secondary to proteinuria
    - 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
    - Hyperlipidemia
        - Likely due to increased hepatic production of very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL),

and low-density lipoprotein (LDL) in response to hypoproteinemia

- Diagnostic criteria (must see both)
  - Serum albumin below 3 g/dL
  - 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:
  - Urinalysis
    - Hematuria can occasionally be seen in FSGS but is usually a sign of nephritic syndrome
  - Protein to creatinine ration from first void of morning
    - UPr/Cr greater than 3.0 is consistent with nephrotic syndrome
  - 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
  - Renal biopsy if strong suspicion of pathology other than minimal change disease
- **When to biopsy**
  - 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
  - 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
  - Lower rates of remission seen in patients treated for 12 weeks instead of 8

- 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
    - Pneumococcal vaccination should be given

COMPLICATIONS

- Acute renal failure
    - Usually reversible with restoration of intravascular volume
- Thrombosis
    - Secondary to urinary losses of antithrombin III and protein S
- Infection
    - 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
    - Generally will progress to end-stage renal disease requiring dialysis and kidney transplant

References

1. Gordillo R, and A Spitzer. 2009. "The nephrotic syndrome". *Pediatrics in Review / American Academy of Pediatrics.* 30 (3): 94-104.

2. Lennon, R., L. Watson, and N.J.A. Webb. 2010. "Nephrotic syndrome in children". *Paediatrics and Child Health.* 20 (1): 36-42.

3. Gipson D.S., Powell L., Massengill S.F., Yao L., et al. 2009. "Management of childhood onset nephrotic syndrome". *Pediatrics.* 124 (2): 747-757.

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