Pediatrics

Nephrotic Syndrome and Proteinuria

Definition

Nephrotic syndrome is characterized by

- Persistent heavy proteinuria (mainly albuminuria) → >2g/m^2/24hr
- Hypoproteinemia → <3g/dL
- Hypercholesterolemia → 250mg/dL
- Edema

Proteinuria

1. <4mg/m^2/hr or $U_{Pr/Cr}$ <0.2 → Normal in kids
2. >40mg/m^2/hr or $U_{Pr/Cr}$ >2.0 → Nephrotic Proteinuria
3. In between these values considered as mild/moderate proteinuria

Types of Proteinuria

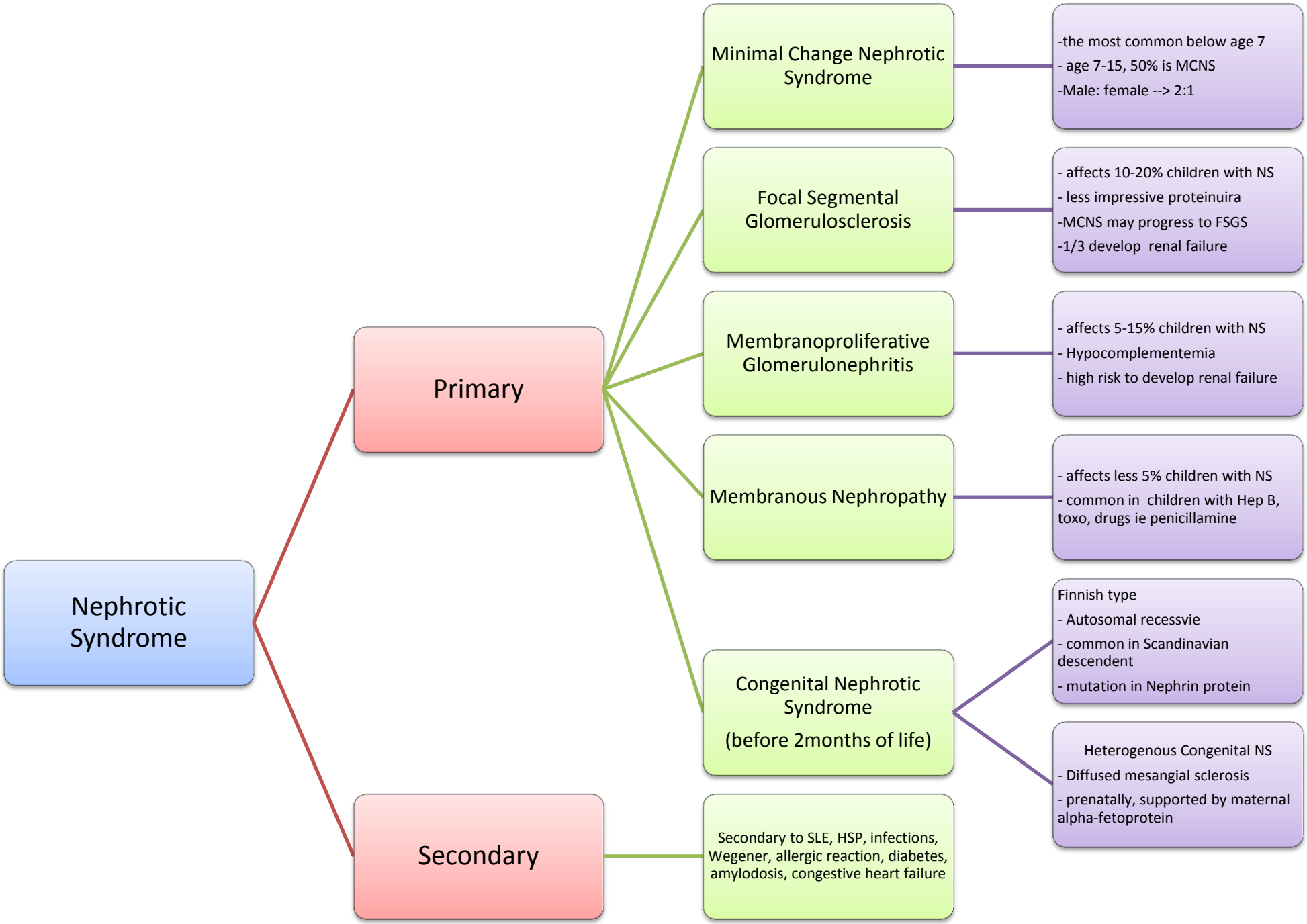
1. Transient or Persistent
2. Asymptomatic or Symptomatic
3. Orthostatic or Fixed
    a. Orthostatic → present in upright position not in recumbent
    b. Fixed → present in all position
4. Glomerular or Tubular
    a. Glomerular → due to disruption of glomerular barrier to filter protein
    b. Tubular → due to increased filtration, impaired reabsorption/ secretion of protein

Pathophysiology

- Increased in protein glomerular filtration is due to
    - Alteration of glomerular basement membrane protein
    - Loss of negative charges that restricts filtration of protein
- Massive proteinuria leads to reduction in serum albumin level
- Eventually leads to diminish of plasma oncotic pressure that leads to fluid shifts into interstitial compartment
- Edema is enhanced by
    - Reduction in circulating blood volume
    - Increased in tubular sodium reabsorption secondary to activation of RAAS
- Hypoproteinemia stimulates liver to increase in hepatic lipoprotein production and reduction in lipoprotein metabolism
    - This results in increased in serum level of lipids (cholesterol and TG)

Nephrotic Syndrome Etiology

1. **Primary Nephrotic Syndrome**
    a. Minimal Change Nephrotic Syndrome
    b. Focal Segmental Glomerulosclerosis
    c. Membranoproliferative Glomerulonephritis
    d. Membranous Nephropathy
    e. Congenital Nephrotic Syndrome
2. **Secondary Nephrotic Syndrome**
    a. Secondary to SLE, HSP, Hep C, diabetes, amyloidosis, renal vein thrombosis, etc


Nephrotic Syndrome
Primary
Secondary
Minimal Change Nephrotic Syndrome
-the most common below age 7
- age 7-15, 50% is MCNS
-Male: female --> 2:1
Focal Segmental Glomerulosclerosis
- affects 10-20% children with NS
- less impressive proteinuira
-MCNS may progress to FSGS
-1/3 develop renal failure
Membranoproliferative Glomerulonephritis
- affects 5-15% children with NS
- Hypocomplementemia
- high risk to develop renal failure
Membranous Nephropathy
- affects less 5% children with NS
- common in children with Hep B, toxo, drugs ie penicillamine
Congenital Nephrotic Syndrome
(before 2months of life)
Finnish type
- Autosomal recessvie
- common in Scandinavian descendent
- mutation in Nephrin protein
Heterogenous Congenital NS
- Diffused mesangial sclerosis
- prenatally, supported by maternal alpha-fetoprotein
Secondary to SLE, HSP, infections, Wegener, allergic reaction, diabetes, amylodosis, congestive heart failure

Clinical Manifestations

1. Sudden onset of
    a. Pitting edema
    b. Ascites
2. Anorexia
3. Malaise
4. Abdominal pain in significant ascites
5. Blood pressure
    a. 25% elevated during presentation
    b. Hypotension and acute tubular necrosis may occur in
        i. Sudden decline in serum albumin
        ii. Significant volume depletion
6. Diarrhea → due to interstitial edema
7. Respiratory distress
    a. Pleural effusion
    b. Pulmonary edema
8. MCNS is characterized by ABSNECE of
    a. Hematuria
    b. Renal insufficiency
    c. Hypertension
    d. Hypocomplementemia

Investigations

- **Urinalysis**
    - >1+ in two or three occasions is considered persistent and should be investigated
- **$U_{Pr/Cr}$**
    - >0.2 on first morning specimen excludes orthostatic proteinuria
    - >2.0 indicates nephrotic syndrome
- **Lipid profile**
    - Elevated TG and cholesterol (>250mg/dL)
- **Liver function test**
    - Serum albumin level → <3g/dL
- **Serum complement level**
    - C3 level reduction implies lesion other than MCNS
    - Therefore RENAL BIOPSY is INDICATED before initiation of steroid therapy
- **UFEME**
    - Microscopic hematuria may presence in 25% of MCNS but doesn't imply response to steroid
- **Blood Urea and Nitrogen**
- **Renal biopsy in indicated in**
    - Steroid non-responders
    - Hypocomplementemia

Treatment

1. 80% of children less than 13 years old with primary NS have steroid responsive NS (MCNS)
    a. Steroid therapy is initiated before renal biopsy in child with typical NS features
2. **Dosing**
    a. Prednisolone 2mg/kg/day (60mg/m^2/24hrs, max 60mg/day) for 12weeks
    b. Divided in 2 or 4 doses per day
    c. 90% respond within 4 weeks
3. **For non-responders**
    a. Renal biopsy is indicated as it may not be MCNS
4. MCNS with frequent relapse and steroid resistance necessitates additional immunosuppressive therapy
5. **Other NS**

a. **FSGS**
    i. No clear effective therapy
    ii. 35% respond to steroid
    iii. Others with immunosuppressive therapy
b. **MPGN and MP**
    i. Need lifelong chronic steroid therapy or immunosuppressive therapy
c. **Congenital NS**
    i. Aggressive medical therapy
    ii. Early
        1. Nephrectomy
        2. Dialysis
        3. Transplantation

6. **Treatment of Edema**
    a. Salt restriction is the mainstay of management
    b. Severe edema may require loop diuretics
    c. If not respond to any of these
        i. Cautious parenteral 25% albumin (0.5-1.0% g/kg within 1-2 hours) with IV loop diuretic
            1. Salt restriction should be continued
7. **Pleural effusion → drainage**
8. **Hypertension**
    a. Beta blockers
    b. Calcium channel blocker
    c. ACE inhibitor

Complications

1. Infections is the major complication
    a. Peritonitis
    b. Bacteremia
    c. Particularly
        i. Kliebsiella sp
        ii. Streptococcus pneumonia
        iii. E.coli
    d. Due to loss of immunoglobulins and complement proteins
2. Steroid side effects in steroid dependent patients
    a. Cushing syndrome
    b. Osteoporosis
    c. Recurrent opportunistic infections
3. Hypovolemia as result from third space loss and diuretic use
4. DIVC/ Thromboembolism
    a. Due to loss of
        i. Coagulation factors
        ii. Antithrombin
        iii. Plasminogen
    b. Warfarin/ low dose aspirin may be indicated in patient with higher risk to develop DIVC
5. Atherosclerotic vascular disease
    a. Due to hypercholesterolemia

Differential Diagnosis			

Transient Proteinuria	• Can be due to
	  ○ Vigorous exercise
	  ○ Fever
	  ○ Significant dehydration
	  ○ Seizures
	• Mild proteinuria. $U_{Pr/Cr}$ <1
	• Glomerular in origin
	• Resolves within few days
		Postural/ Orthostatic Proteinuria	• Benign condition
			• Normal protein secretion during recumbent position, but significant proteinuria during upright position
			• Glomerular in nature
			• More common in
			  ○ Adolescent
			  ○ Tall and thin person
			• Not associated with progressive disease

Tubular Proteinuria	• Preponderance of low molecular weight protein in urine
	• Typically suspected in
	  ○ ATN
	  ○ Pyelonephritis
	  ○ Structural renal disorder
	  ○ Polycystic kidney
	  ○ Antibiotics
	  ○ Chemotherapy drugs
	• Fanconi Syndrome
	  ○ Tubular proteinuria
	  ○ Tubular electrolyte wasting
	  ○ Glycosuria
		Glomerular Proteinuria	• Combination of large and small molecular weight proteins in the urine
			• Variable level of proteinuria
			• Often with evident glomerular disease
			  ○ Hematuria
			  ○ Red cells cast
			  ○ Hypertension
			  ○ Renal insufficiency
			• Causes
			  ○ Hemolytic uremic syndrome
			  ○ Crescentric glomerulonephritis
			  ○ Poststreptococcus glomerulonephritis
			  ○ Lupus nephritis