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L2:Types of proteinuria

Transient proteinuria:

It occurs in approximately 10% of children, it is more common in adolescent than in younger children. It characterized by positive test for proteinuria by urinary dipsticks but it will resolve with repeated dipsticks tests with normal urinary protein excretion.

The cause is unclear, but it might associated with fever >38.3°C (101°F), exercise, dehydration, cold exposure, heart failure, seizures, or stress.
Transient proteinuria usually does not exceed 1+ or 2+ on the dipstick.
It is benign condition, no evaluation or therapy is needed.

Orthostatic (Postural) proteinuria:

Is the most common cause of persistent proteinuria in school-age children and adolescents, occurring in up to 60% of children with persistent proteinuria. The child is usually asymptomatic, and the condition is discovered by routine urinalysis.
Patients with orthostatic proteinuria excrete normal or minimally increased amounts of protein in the supine position, while in the upright position, urinary protein excretion may be increased 10-fold, up to 1,000 mg/24 hr (1 g/24 hr).
There are no Hematuria, hypertension, hypoalbuminemia, edema, and renal dysfunction.

No further evaluation is necessary, and the patient and family should be reassured of the benign nature of this condition.

The cause of orthostatic proteinuria is unknown, but increased body mass index is recognized as a strong correlation factor.
Patients should be monitored for the development of non-orthostatic proteinuria, particularly in the presence of hematuria, hypertension, or edema which may indicate underlying kidney disease.

Nephrotic syndrome (NS)

It is a glomerular diseases characterizes by heavy (nephrotic-range) proteinuria which cause hypoalbuminemia (≤2.5 g/dL), edema, and hyperlipidemia (cholesterol >200 mg/dL).
Nephrotic range proteinuria is defined as proteinuria >3.5 g/24 hr or a urine protein : creatinine ratio >2.

Nephrotic syndrome affects 1-3 per 100,000 children <16 yr of age. Without treatment, nephrotic syndrome in children is associated with a high risk of death, most commonly from infections.

Causes of nephrotic syndrome:

I. Idiopathic (primary) nephrotic syndrome:

1. Minimal change disease.
2. Focal segmental glomerulosclerosis.
3. Membranous nephropathy.

II. Congenital NS:

1. Finnish-type congenital nephrotic syndrome (absence of nephrin)
2. Denys-Drash syndrome (mutations in WT1 transcription factor)
3. Congenital nephrotic syndrome with lung and skin involvement
4. Mitochondrial disorders
5. Metabolic Disorders With or Without Nephrotic Syndrome: Alagille syndrome α1-Antitrypsin deficiency, Glycogen storage disease, Sickle cell disease

III. Secondary NS:

1. Infections: Endocarditis, Hepatitis B and C, HIV-1, Infectious mononucleosis, Malaria, Syphilis (congenital and secondary), Toxoplasmosis,
2. Drugs: Captopril, Penicillamine, Gold, NSAID drugs, Interferon, Mercury, Heroin Lithium
3. Immunologic or Allergic Disorders: Vasculitis syndromes, Food allergens, Serum sickness.
4. Associated With Malignant Disease: Lymphoma, Leukemia, Solid tumors.

Pathogenesis:

The underlying abnormality in nephrotic syndrome is an increased permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia. This increase permeability is might due to **abnormal function of the podocytes** which are epithelial cells located on the outside of the glomerular capillary loops which is the major component of the glomerular filtration barrier to proteins or it due to not fully understand **immune mechanism**.

Mechanisms of clinical manifestations of NS:

1. Edema:

Is the most common presenting symptom of children with nephrotic syndrome. It is universal in all patients, but the exact mechanism of edema formation is remain uncertain. There are 2 opposing theories:

A. The *underfill* hypothesis: is based on the fact that nephrotic-range proteinuria leads to a fall in the plasma protein level which decrease the intravascular oncotic pressure. This leads to leakage of plasma water into the interstitium, causing edema.

As a result of reduced intravascular volume, there is increased secretion of vasopressin and atrial natriuretic factor, which, along with aldosterone, result in increased sodium and water retention by the tubules which then leaked to interstitial tissues and causing more edema.

This hypothesis does not explain the clinical picture of some patients with edema caused by nephrotic syndrome who have clinical signs of intravascular volume overload and not volume depletion.

B. The *overfill* hypothesis postulates that nephrotic syndrome is associated with primary sodium retention as a result of abnormality in the sodium channels in the distal tubules , with subsequent volume expansion and leakage of excess fluid into the interstitium.
The clinical weaknesses of this hypothesis are that numerous nephrotic patients are presented with an obvious clinical picture of IV volume depletion such as low blood pressure, tachycardia, and elevated hemoconcentration. Furthermore, amiloride, which is sodium channel blocker, is not sufficient to induce adequate diuresis if use alone.

2. Hyperlipidemia:
Serum lipid levels (cholesterol, triglycerides, low-density lipoprotein, and very-low-density lipoproteins) are elevated In nephrotic syndrome for 2 reasons.

- **a.** Hypoalbuminemia stimulates generalized hepatic protein synthesis, including synthesis of lipoproteins.
- **b.** Urinary losses of lipoprotein lipase which is responsible for lipid catabolism.

3. Increased susceptibility to infections:
Patients with nephrotic syndrome are at increased risk of infections (sepsis, peritonitis, pyelonephritis), especially with encapsulated organisms such as Streptococcus pneumoniae (most common MO) and Haemophilus influenza and Gram-negative bacteria e.g. E. coli. The cause might be due to:

A. Urinary loss of C3, C5 and C3b, properdin factor B, and immunoglobulins.
B. Use of immunosuppressive medications in treatment of nephrotic syndrome.
C. Malnutrition
D. Edema or ascites acting as a potential culture medium.

4. Hypercoagulability:
NS is a hypercoagulable state resulting from multiple factors such as vascular stasis from hemoconcentration and intravascular volume depletion, increased platelet number and aggregability, increase hepatic production of fibrinogen and other clotting factors and urinary losses of antithrombotic factors such as antithrombin III and protein S. Hypercoagulation manifest as deep venous thrombosis. and arterial

Congenital Nephrotic Syndrome:

Is defined as nephrotic syndrome manifesting at birth or within the *1st 3 mo of life*.

Classification:

I. Primary Congenital NS(Inherited autosomal recessive disorders):

1. **Finnish-type** (absence of nephrin). Affected infants present at birth with edema and enlarged placenta (>25% of the infant's weight). Prenatal diagnosis can be made by elevated maternal and amniotic α-fetoprotein levels.

2. **Denys-Drash syndrome** (abnormal podocyte function). Patients present with early-onset nephrotic syndrome, progressive renal insufficiency, ambiguous genitalia, and Wilms tumors.
3. **Pierson syndrome:** include congenital NS and bilateral microcoria (fixed narrowing of the pupil).

II. Secondary Congenital NS: such as in:

1. Congenital infections (CMV, syphilis, hepatitis B and C, HIV)
2. Infantile systemic lupus erythematous (SLE)
3. Exposure to mercury.

Clinical Features:

Severe generalized edema, poor growth and nutrition, hypoalbuminemia, increased susceptibility to infections, hypothyroidism (from urinary loss of thyroxin-binding globulin), and increased risk of thrombosis

Prognosis: is very poor and most infants have progressive renal insufficiency

(primary) Idiopathic Nephrotic Syndrome

Its occur in approximately 90% of children with nephrotic syndrome. Is associated with primary glomerular disease without an identifiable causative disease or drug.

Histological types:

1. Minimal change nephrotic syndrome (MCNS): occur in approximately 85% of total cases of nephrotic syndrome in children, the glomeruli appear normal or show a minimal increase in mesangial cells and matrix.
More than 95% of children with minimal change disease respond to corticosteroid therapy.

2. Mesangial proliferation: (10-20% of primary NS) is characterized by a diffuse increase in mesangial cells and matrix on light microscopy. Approximately 50% of patients with this histologic lesion respond to corticosteroid therapy.

3. Focal segmental glomerulosclerosis (FSGS): (5-15% of primary NS) There is mesangial cell proliferation and segmental scarring on light microscopy. Only 20% of patients with FSGS respond to prednisone. The disease is often progressive, ultimately involving all glomeruli, and ultimately leads to end-stage renal disease in most patients.