NEPHROTIC SYNDROME

NS is the clinical manifestation of glomerular diseases associated with heavy proteinuria (nephrotic-range). 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

NS is characterized by:

- ✓ ***Heavy proteinuria***
- ✓ ***Hypoalbuminemia***
- ✓ ***Edema***
- ✓ ***Hyperlipidemia.***

NS can be divided into: 1- Idiopathic (most *common)*

2- Secondary to other diseases or syndromes

3- Congenital

Idiopathic Nephrotic Syndrome:

Approximately 90% of children with nephrotic syndrome have idiopathic NS

It is divided into the following pathological types

1. Minimal Change NS; characterized by effacement "fusion" of the epithelial cell foot processes. (approximately 85% of total cases of nephrotic syndrome in children)

2. Focal Segmental Glomerulosclerosis; characterized by mesangialproliferation and segmental scarring.

3. Membranous Nephropathy; characterized by thickening of basement membrane with subepithelial deposits.

4. Other types include: Mesangial Proliferation & Membranoproliferative GN (type 1, 2).

CLINICAL CONSEQUENCES OF NEPHROTIC SYNDROME

• Proteinuria & Hypoalbuminemia is due to increase permeability of the glomerular capillary wall.

• Edema is due to hypoalbuminemia which decreases plasma oncotic pressure and --transudation of fluid from the intravascular compartment to the interstitial space. The reduction in intravascular volume decreases renal perfusion pressure leads to activation of renin-angiotensin-aldosterone system & atrial natriuretic factor → increase reabsorption of sodium & water.

However, this theory does not apply to all patients with NS.

The other hypothesis postulates that NS is associated with primary sodium retention, with subsequent volume expansion and leakage of excess fluid into the interstitium.

• Hyperlipidemia is due to hepatic lipoprotein synthesis (stimulated by hypoalbuminemia) combined with decrease lipid catabolism due to urinary loss of lipoprotein lipase.

Clinical manifestations:

Age : usually occur between 2-6 yr.(MCNS),

whereas FSGS is tend to occur in older children.

The initial episode and subsequent relapses may follow minor infections or sometimes insect bite.

Children usually present with mild periorbital& lower extremities edema. Then edema becomes generalized with development of ascites, pleural effusions, and

genital edema ,Other symptoms include: irritability, anorexia, abdominal pain & diarrhea

D.Dx

I. Glomerulonephritidis.
II. Protein-losing enteropathy.
III. Protein malnutrition (kwashiorkor)
IV. Hepatic failure .
V. Congestive HF.

INVx:

• GUE for Proteinuria (3+ or 4+) or(> 40 mg/m2/hr.) or (>150 mg/kg/hr.).

• Urinary protein/creatinine ratio (1st voiding at morning) >2.

• Serum Albumin <2.5 g/ dL.

• Serum Cholesterol & Triglyceride·(cholesterol >200 mg/dL).

• Serum Urea & Creatinin, C3 & C4 are typically normal.

• Renal Biopsy is not routinely indicated unless :

Age <1 yr. or >8 yr.
Family hx of renal disease,
Extrarenal findings (arthritis, rash, anemia),
Hypertension , Pulmonary *edema*
Hematuria
Renal insufficiency
Hypocomplementemia
Resistance to steroid Rx.

Treatment

Corticosteroids are the cornerstone in Rx of NS; Prednisone orally 60 mg/m2/day (max. 80) as single dose in morning for 4-6 wk,then the dose should be tapered to 40 mg/m2 every other day for at least 4 *wk.,* then further tapered & stopped over the next 1-2 mo. *(* total 3-4 mo.).

The response to steroid usually occur within 2-4 wk. of daily steroid Rx

(-ve or trace proteinuria for 3 consecutive days).

• Children with 1st episode with mild to moderate edema can be managed as *outpatient* by the following (in addition to prednisone):-

1. Salt intake *"No added salt".*

2.Diuretics orally should be used with caution due to the risk of thromboembolism.

• Children with severe edema, should be *hospitalized* & managed by the following (in addition to prednisone):-

1. Fluid restriction (in addition to sodium restriction) may be necessary if the child is hyponatremic. Swollen scrotum may be elevated. ·

2. Diuretics e.g. furosemide orally or IV, 1-2 *mg/kg/dose.*

3. If the above measures are not effective, give 25% albumin IV (0.5-1 *g/kg/dose)* slowly followed by furosemide.

- Rx of relapse is by the same dose of prednisone until remission, then tapering the dose over 4-8 wk. whereas patients who are frequent relapsers, steroid dependent or resistant or children suffer from severe SE of corticosteroids are candidate for alternative agents such as Cyclophosphamide, Cyclosporine.

• ACE inhibitors & Angiotensin II blockers may be helpful as adjunct Rx to decrease proteinuria in steroid-resistant patients.

Complications:

1• *Infection;* it is the major Cx of NS, it is mainly due to immune deficiency. Spontaneous bacterial peritonitis is the most frequent infection, although sepsis, pneumonia, cellulitis, and UTI may also occur. *S. pneumoniae* is the most common organism causing peritonitis as well as other Gram -ve bacteria e.g. *E. coli.*

Vaccinations, especially "polyvalent" pneumococcal, varicella & influenza vaccines can be given during remission or low dose alternate day steroids.

Note: Corticosteroid Rx usually masks fever and other signs of inflammation, thus it need high index of suspicion for infection combined with aggressive Rx after Dx.

2 • *Thromboembolism;* it is uncommon Cx due to high prothrombotic factors (fibrinogen level, thrombocytosis, hemoconcentration, relative immobilization) and *low* fibrinolytic factors (urinary losses of antithrombin III, proteins C and S), thus overaggressive diuresis should be avoided .Anti-coagulation Px is not recommended unless there is previous thromboembolic event.

3• *Hyperlipidemia;* CVS events e.g. MI is rare in children.

4• *Psychological effects;* patient with NS should not be considered as an "ill person", especially during remission.

Secondary Nephrotic Syndrome

1. Glomerular diseases may have a nephrotic component e.g. Membranous nephropathy; Membranoproliferative GN, PostinfectiousGN , SLE, and HSP

2. Infections & infestation e.g. HBV, HCV, HIV, Malaria and Schistosomiasis.

3. Drugs e.g. NSAIs, Penicillamine, Captopril, Phenytoin, Gold & Lithium.

4. Malignancy e.g. Lymphoma & Leukemia (but mainly in adults).

5. Syndromes that may associated with NS include: Alport syndrome, Hurler syndrome, Alagille syndrome, Glycogen storage disease .... Etc.

Congenital Nephrotic Syndrome

It is NS that appear at birth or within the 1st 3 mo. of life.

Causes of congenital NS include:-

- *Finnish-Type NS:* It is the most common cause of congenital NS &

inherited as AR. It is manifested in utero as fetal hydrops, large placenta, high *a* fetoprotein, prematurity, respiratory distress, hypothyroidism and separation of cranial sutures.

The disease is persistent edema and progressive renal failure with death by age of 5 yrs.

Rx. Aggressive nutrition , ACE inhibitor, IV albumin, IVIG, unilateral (or bilateral) nephrectomy, chronic dialysis, and kidney transplantation; whereas corticosteroids & immunosuppressive are of no value in Finnish-type NS.

- *Congenital Infections* e.g. TORCHS can cause congenital NS.

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