Nephrotic Syndrome

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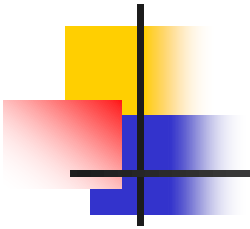


Proteinuria

Urine Dipstick test

urine dipstick test or R&M

- negative or trace (150 mg/L) …..normal
- 1+ (300 mg/L),
- 2+ (1000 mg/L),
- 3+ (3000mg/L),
- 4+ (20000 mg/L).

Proteinuria

- **False-positive** test results may be seen in patients with gross hematuria,
- contamination with antiseptic agents (chlorhexidine and benzalkonium chloride),
- urinary pH greater than 7.0
- **False-negative** test occur with dilute urine or when the predominant urinary protein is not albumin

Diagnosis Proteinuria

- A *positive dipstick* is considered if it reads +1 (300mg/L) or more in non concentrated urine
- **A (24 hr) urine collection** is the best method of quantitation of urinary protein

The limit of normal protein excretion in healthy children is 0.15 g/24 hr or

< 4 mg/m2/hr *in a 24h urine collection.*

Proteinuria in Children

- Abnormal protein excretion is defined as 4–40 mg/m2/hr,
- ***Nephrotic range*** is defined as more than 40 mg/m2/hr *or* 50mg/kg in 24h collection

Other tests

- on a urine sample ; a **<u>Upr/Ucr ratio :</u>**

  Normal < 20mg/mmol or 0.2 mg/mg

  Nephrotic range > 200mg/mmol or 2 mg/mg

Causes of Proteinuria

- **TRANSIENT PROTEINURIA**
  - Fever
  - Exercise
  - Dehydration
  - Cold exposure
  - Congestive heart failure
  - Seizure
  - Stress

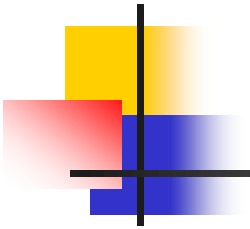
Causes of Proteinuria

- **ORTHOSTATIC (POSTURAL) PROTEINURIA**

- **GLOMERULAR DISEASES**
  Focal segmental glomerulosclerosis
  Mesangial proliferative glomerulonephritis
  Membranous nephropathy
  Membranoproliferative glomerulonephritis
  Lupus nephritis
  IgA nephropathy
  Henoch-Schönlein purpura nephritis
  Amyloidosis
  Diabetic nephropathy

Causes of Proteinuria

- **TUBULAR DISEASES**
  Cystinosis
  Wilson disease
  Lowe syndrome
  Galactosemia
  Tubulointerstitial nephritis
  Heavy metal poisoning
  Acute tubular necrosis
  Renal dysplasia
  Polycystic kidney disease
  Reflux nephropathy



NEPHROTIC SYNDROME

Nephrotic Syndrome

It *is characterised by*

- Heavy proteinuria (>3.5 g/24 hr in adults or >40 mg/m2/hr in children),
- Hypoalbuminemia (<2.5 g/dL),
- Edema
- Hyperlipidemia.

Etiology

(90%) of nephrotic syndrome in children is a form of the

idiopathic nephrotic syndrome (INS)

while (10%) is secondary .

INS

Idiopathic NS

- is glomerular diseases intrinsic to the kidney and not related to systemic causes
- incidence is 2–3/100,000

- Minimal change disease (85%)
- Mesangial proliferation (5%),
- Focal segmental glomerulosclerosis (10%).

secondary NS are related to other GN

- Membranoproliferative GN (MPGN)
- Membranous nephropathy

Secondary Nephrotic Syndrome

- Patients usually aged > 8 yr
- Hypertension, hematuria, renal dysfunction,
- extrarenal symptomatology (rash, arthralgias)
- low serum complement levels

Secondary Nephrotic Syndrome

Causes :

- GN

lupus nephritis LN,

Henoch-Schönlein nephritis

Postinfectious glomerulonephritis

Secondary Nephrotic Syndrome

- Infections:

  malaria and schistosomiasis

  hepatitis B virus, hepatitis C virus, and HIV.

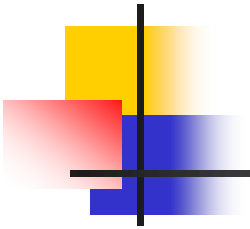
- Drugs and Chemicals :

  Membranous (penicillamine, captopril, gold, nonsteroidal anti-inflammatory drugs)

  Minimal Change disease (ethosuximide,, lithium)

- Malignancies :

  Hodgkin Lymphoma, lung and GIT cancers



Pathophysiology of NS

Pathopysiology

Edema :

- An increase in permeability of the glomerular capillary wall, which leads to massive proteinuria and hypoalbuminemia
- Hypoalbuminemia causes a decrease in the plasma oncotic pressure ,and fluid transudation from the intravascular compartment to the interstitial space…leads to edema

Pathopysiology

Elevated Lipid levels (cholesterol, triglycerides) :

- Hypoalbuminemia stimulates generalized hepatic protein synthesis, including synthesis of lipoproteins.
- Lipid catabolism is diminished

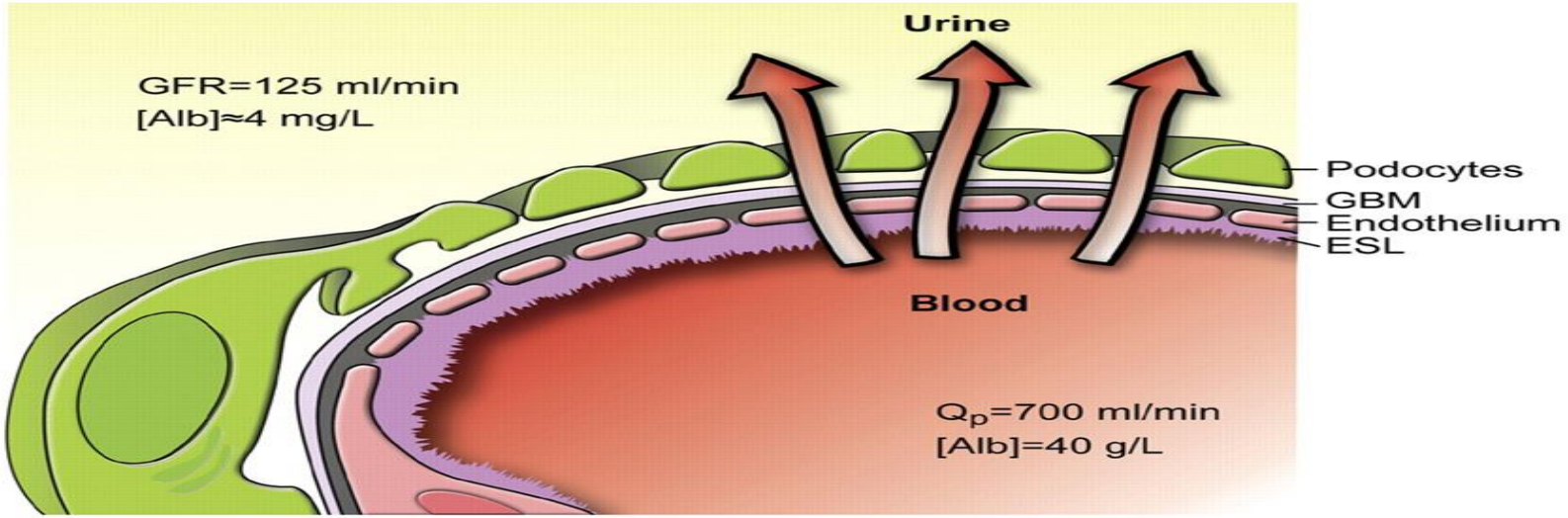
Pathophysiology of proteinuria in renal disease

Proteinuria:

Exciting development in recent years in understanding the pathophysiology of nephrotic syndrome has occurred in the area of Podocyte biology and the glomerular filtration barrier.

The Glomerular Filtration Barrier

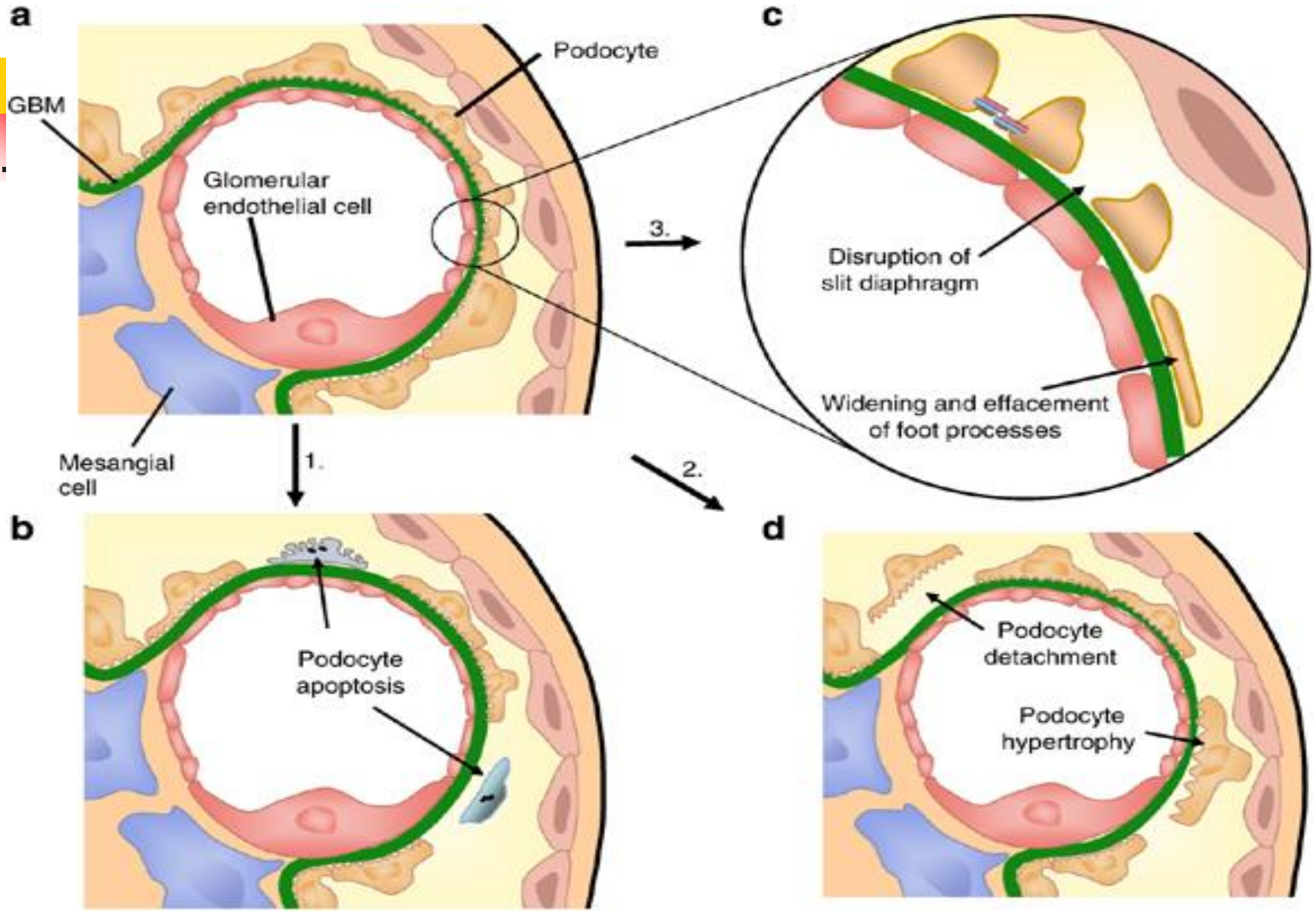
- fenestrated capillary endothelium,
- extracellular basement membrane, and
- intercalated podocyte foot processes, connected by 35-45 nm slit diaphragms.



Pathopysiology

Nephrotic syndrome is associated with fusion (effacement) of podocyte foot processes.

This effacement of the podocytes long was thought to be a secondary phenomenon of nephrotic syndrome


a
GBM
Podocyte
Glomerular endothelial cell
Mesangial cell
1.
2.
3.
b
Podocyte apoptosis
c
Disruption of slit diaphragm
Widening and effacement of foot processes
d
Podocyte detachment
Podocyte hypertrophy

Pathopysiology

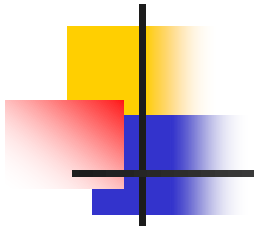
Genetics :-

Theories have shifted towards the podocyte as playing a primary role in the development of proteinuria.

-The understanding of proteinuria expanded with insights into the **molecular biology** of the podocyte.

-Various forms of INS associated with **mutations in podocyte genes,** with the slit-diaphragm and podocyte cytoskeleton proetiens (nephrin and podocin)

-several gene mutations identified are involved in SRNS and Congenital NS (*NPHS1,NPHS2, TRCP6, CD2AP, ACTN4)*; the glomerular basement membrane (*LAMB2*); mitochondria (*COQ2*); and transcription factors (*WT1, LMX1B*).[7]



Minimal Change Disease

MCD clinical picture

- 100% nephrotic
- 10-20% hematuria
- 10% hypertension
- Doesn't progress to end stage renal failure
- 90% response to steroids

Minimal Change Disease MCD

- It is more common in males than in females (2:1)
- Frequency 75% in children, 15% in adults
- appears between the ages of 2 - 6 yr
- Present with edema, which is initially noted around the eyes and in the lower extremities
- edema may become generalized, with the development of ascites, pleural effusions, and genital edema .
- *hypertension and gross hematuria are uncommon*

History

-edema

-SOB, cough , chest pain

-abdominal pain

-diarreoha and vomiting

-first presentation /relapse…..age at dx , trigger URTI ?

-treatment and medications received

-blood transfusions, infections (hep B,C)

-arthritis , ulcers , skin rash

-Hematuria

-Headache and blurred vision

Exam

-general condition

-vital signs (BP …orthosotatic changes)

-edema pitting

-cardiac and chest exam

-abdomen exam

Idiopathic NS

Differential diagnosis:

- protein-losing enteropathy,
- hepatic failure,
- congestive heart failure,
- Other chronic glomerulonephritis, and protein malnutrition

Investigations

-Urine R&M .. For protein and RBC

-**24h urine collection or Upr/ucr ratio**

-Urine culture

-Serum albumin

-KFT

-CBC

-C3 and C4 level

-HBV and HCV serology

-ANA , DS-DNA and AsO titre if needed

- **Renal Biopsy** is only needed with Atypical presentation:

  hematuria (gross)

  hypertension,

  renal insufficiency,

  hypocomplementemia

  age < 1yr or > 12yr

Diagnosis MCD summary

- Urinary protein excretion in the nephrotic range (exceeds 40 mg/m2/hr) in children
- microscopic hematuria may be present in 20% of children
- serum albumin is < 2.5 g/dL,
- Serum creatinine value is usually normal
- increased serum cholesterol and triglyceride
- C3 and C4 levels are normal.
- Renal biopsy is not required for diagnosis in most children with Idiopathic nephrotic syndrome ..(MCD)

Pathology ***Minimal change disease***

- ***Minimal change disease*** (85%):

  light microscopy glomeruli appear normal or show a minimal increase in mesangial cells and matrix.

  Immunofluorescence : are negative,

  Electron microscopy simply reveals effacement of the epithelial cell foot processes.

Pathology

- ***Focal segmental glomerulosclerosis*** (10% of total cases)

glomeruli show mesangial proliferation and segmental scarring on light microscopy .

immunofluorescence microscopy shows IgM and C3 staining.

Electron microscopy shows segmental scarring of the glomerular tuft with obliteration of the glomerular capillary lumen.

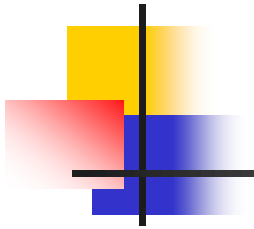
Pathology

- ***Mesangial proliferation***

diffuse increase in mesangial cells and matrix on light microscopy.

Immunofluorescence microscopy shows mesangial IgM and/or IgA staining.

Electron microscopy reveals increased numbers of mesangial cells and matrix as well as effacement of the epithelial cell foot processes.



TREATMENT

Treatment

- Education of the family
- Salt and sodium restriction in acute illness
- May use diuretics
- Admission : for those with severe edema, pleural effusion , ascites and scrotal swelling
- Follow daily urine protein and weight

Treatment

Medications :

-Intravenous administration of 25% Albumin

-Steroids

-other immunesuppressive medications eg(cyclophosphamide, cyclosporin)

Treatment

- Steroid therapy:

  can be initiated in children with typical nephrotic presentation within the ages of 2-8 years **without renal biopsy**

Steroid treatment

- Given in dose of 60 mg/m2/day or 2mg/kg/day (maximum daily dose, 60 mg), divided into two to three doses for 4-6 consecutive weeks
- After response the dose will be tapered to EOD dose for another 3 months.
- 80-90% of patients with MCD will respond to steroid , and will do so within the first 4 weeks of treatment (called SSNS)

Steroid Treatment ..response

- **Responsive to steroid** : Urine trace or negative for protein for 3 consecutive days. Those who respond in the first 28 days are called SSNS
- **Steroid Resistant** SRNS : those who continue to have proteinuria (2+ or greater) after full 6 wks of proper steroid therapy
- **Relapse** : 3–4+ proteinuria and edema for >3 days
- ***Steroid Dependent:*** relapse while on taper alternate-day steroid therapy or within 14 days of stopping prednisone therapy
- **Frequent Relapser**: those who have 4 or more relapses in 12 months

SRNS

- All patients with steroid resistant nephrotic syndrome *require a kidney biopsy*
- Causes

  FSGS

  MCD

  MPGN (mesangiocapillary) GN

  Membranous

  DMS (diffuse meningeal proliferation)

  Congenital Nephrotic Syndrome

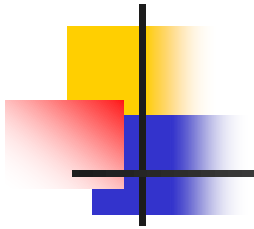
SRNS

- SRNS other than MCD has poor outcome and usually progress to ESRD

Treatment

Steroid-dependent patients, frequent relapser, and SRNS are candidates for other types of therapy:

- Cyclophosphamide (SSNS frequent relapser)
- High dose IV Methypredinson
- Cyclosporine
- Tacrolimus
- MMF
- Rituximab
- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II blockers



COMPLICATIONS

Complications

- Drug Side Effects:

  Steroids : (cushingoid appearance, hypertension, cataracts, and/or growth failure)

  Cyclophosphamide (neutropenia, disseminated varicella, hemorrhagic cystitis, alopecia, sterility

Complications

- **Ciclosporin** (hypertension, nephrotoxicity, hirsutism, and gingival hyperplasia, neutropenia)

Complications

Infections

- Infection is the major complication of nephrotic syndrome
- Increased susceptibility to bacterial infections owing to urinary losses of immunoglobulins and properdin factor B, defective T cell-mediated immunity, immunosuppressive therapy, malnutrition, edema.....

Complications

- Spontaneous bacterial peritonitis is the most frequent type of infection, although sepsis, pneumonia, cellulitis, and urinary tract infections may also be seen.
- *Streptococcus pneumoniae* is the most common organism causing peritonitis, gram-negative bacteria such as *Escherichia coli* may also cause it

Vaccines

- Patients with nephrotic syndrome who are receiving treatment are not immunocompetent , so they should receive polyvalent pneumococcal vaccine, and given varicella vaccine when in remission ,
- Influenza vaccine should be given on a yearly basis.

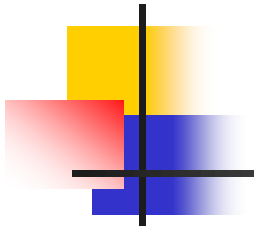
Complications

Thrombosis

- Increased risk of thromboembolic events, both arterial and venous,
- renal vein thrombosis, pulmonary embolus, sagittal sinus thrombosis, and thrombosis of indwelling arterial and venous catheters

Complications

- thrombosis is related to increased prothrombotic factors (fibrinogen, thrombocytosis, hemoconcentration, relative immobilization) and decreased fibrinolytic factors (urinary losses of antithrombin ill, proteins C and S)
- Prophylactic anticoagulation is not recommended in children unless they have had a previous thromboembolic event



PROGNOSIS

Prognosis

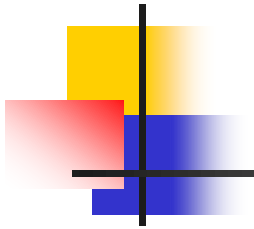
- The disease is not inherited
- The child will remain fertile unless cytotoxic drugs are used
- Children with MCD usually don't progress to end stage renal failure
- When in remission there is no need for diet or activity restriction, or dipstick follow-up

Prognosis

- *90-95% of patients* with MCD will respond to steroids
- Approximately 50% of patients with mesangioproliferative respond to corticosteroid therapy.
- Only 30% of patients with FSGS respond to prednisone.
- 70% of SSNS will have a relapsing course:

50% will be frequent relapser or steroid dependent

- 80% will go into long remission during childhood



Thank You