# LECTURE 4 & 5:

## PATHOLOGY OF THE FIVE MAJOR RENAL GLOMERULAR SYNDROMES

Dr.Najeeb 10 vedioes are very helpful
http://youtu.be/iAQkxTwnDWQ

# OBJECTIVE

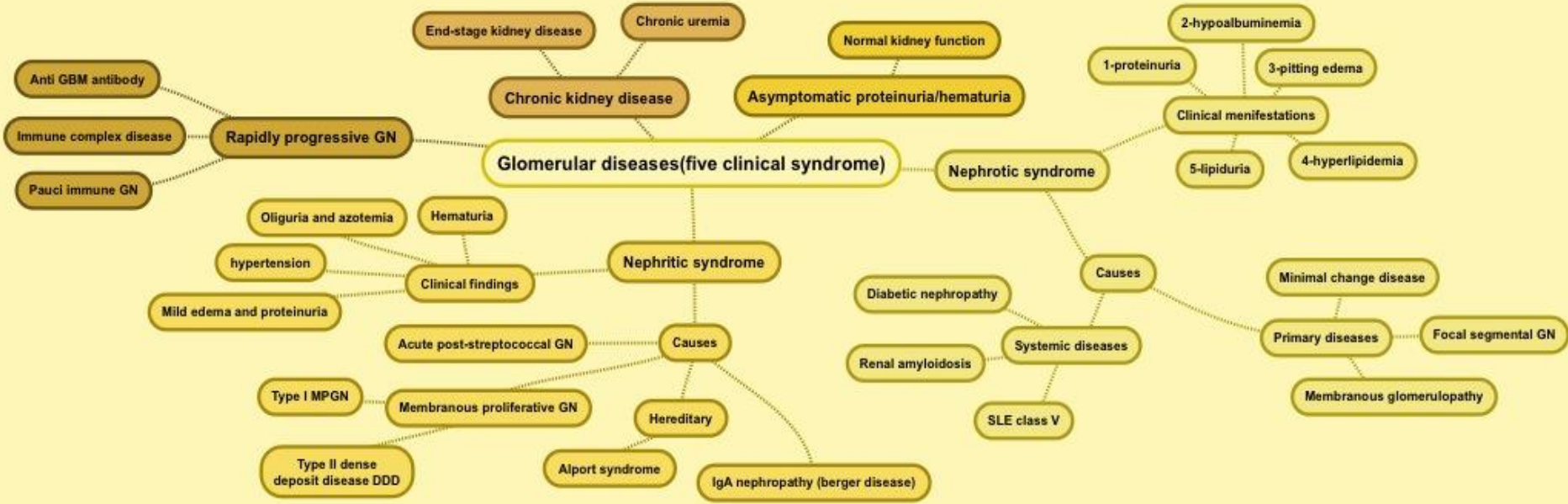
**- At the end of these two lectures student should be able to:**

- Recognize the five major renal clinical syndromes.
- Describe the main differential pathological diagnosis for each syndrome.
- Perform a clinico-pathological correlation.
- Describe the patterns of injury of each syndrome.

For more information you can read:

- **Robbins :** P517 – 533
  P541-542 (chronic kidney disease )

# Mind Map




## Abbreviations that may used

GN = glomerulonephritis
L.M= light microscopy
IF = immunofluorescence
EM = electron microscopy
GBM= glomerular basement membrane

# 1. Nephrotic syndrome (Nephrosis):

A group of conditions characterized by increased Basement membrane permeability.

- Clinical manifestations:

1- Massive Proteinuria (loss more than 3.5g/day).

2- Hypoalbuminemia (less than 3g/dL).

3- Generlaized pitting edema* (Called Anasarca).

- Sites: Specially around the eyes (puffiness) , sometimes edema in hands and foots
- Caused: by losing of proteins (hypoalbuminemia + protienuria) > drop of colloid pressure > fluid moves from blood to tissue.

4- Hyperlipidemia :

- Caused: by loss protein and lipase* > low level of protein in blood > Liver consolidate and increase production of lipoprotein as results , high level of lipid in blood.

5- Lipiduria.

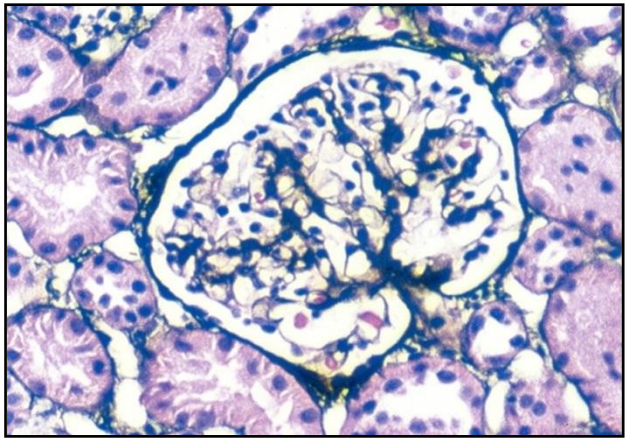
*we can see pitting edema in heart failure also.

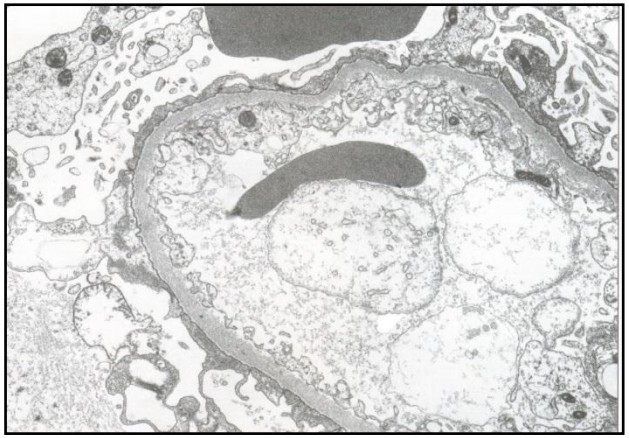
* Lipase is an enzyme which is responsible for lipids catalyse

# CAUSES OF NEPHROTIC SYNDROME:

## Primary kidney diseases :

### A. MINIMAL CHANGE DISEASE:





- More frequent in children (1 – 7 years).
- L.M: The glomeruli are normal (because of that it has this name) + no tubular interstitial fibrosis.
- IF : -ve
- EM: Diffuse effacement*(طمس) of foot processes of the podocytes* + GBM normal
- Prognosis:

90% of children response to short course of corticosteroid.

Adult also response to corticosteroid but slower

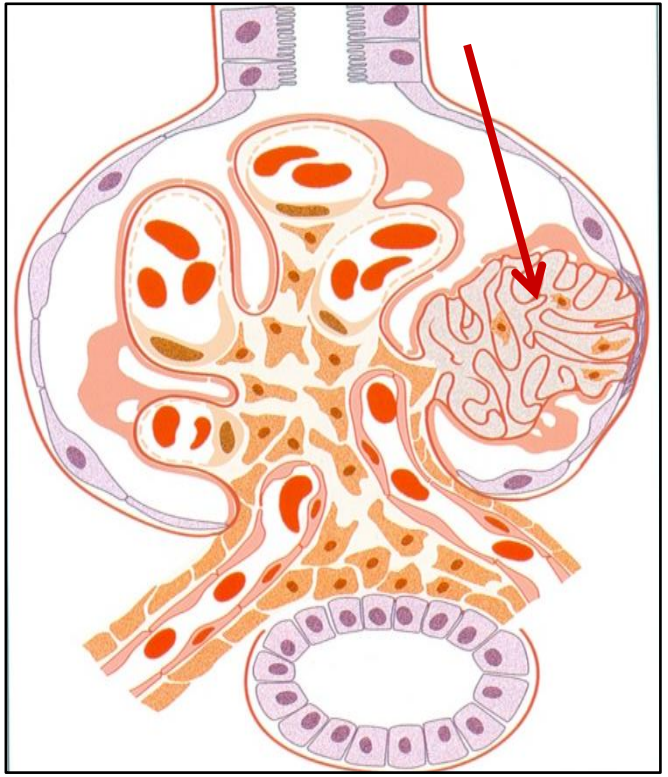
* **Effacement** is the shortening, or thinning, of a tissue.

* Remember any injury in podocyte cause proteinuria

# CAUSES OF NEPHROTIC SYNDROME:

## Primary kidney diseases :

### B. Focal segmental* glomerulosclerosis:



- Common site in glomerulus which found in juxtaglomerular apparatus.
- Usually affect old patient and adult.
- May be primary or secondary :

**1-Primary** (idiopathic).

**2-Secondary to other disease:**

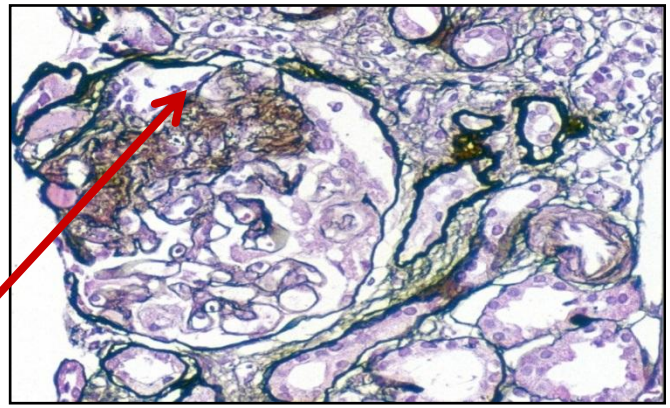
- HIV nephropathy.
- Heroin Injection.
- IgA nephropathy.
- Inherited or congenital "by mutation APO- L1 gene in chromosome 22 which create protein found in filtration barrier"

*Focal = Some glomeruli affected.
Diffuse = All glomeruli are affected
Segmental = Part of one glomerulus is affected.
Global = One glomerulus is entirely affected

# CAUSES OF NEPHROTIC SYNDROME:

## Primary kidney diseases :

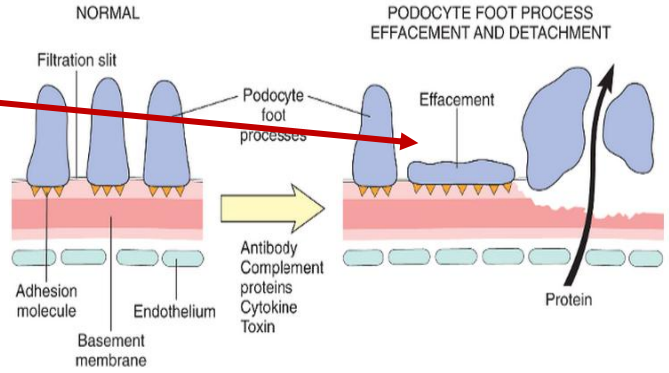
### B. Focal segmental glomerulosclerosis:



- L.M:

1. sharply defined segmental sclerosis (hyaline masses = **hyalinosis** ). This finding proves the disease
2. obliteration of capillary lumina
3. increased mesengial matrix.

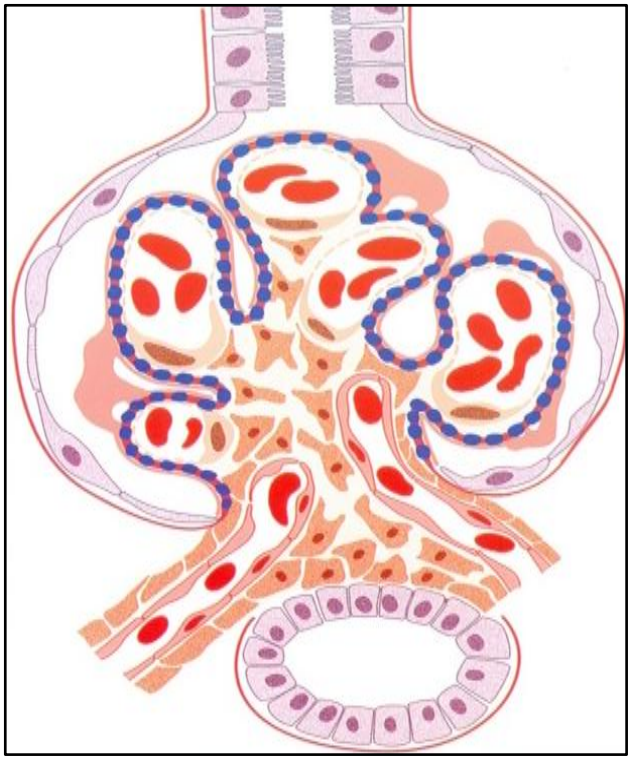
- IF : trapping of **IgM** and complement (**C3**) in GMB and podocytes.
- EM: diffuse effacement(طمس) of foot processes of the podocytes
- Prognosis: 50% of children develop chronic kidney disease
- Progression: leads to global sclerosis + tubular atrophy + interstitial fibrosis.



# CAUSES OF NEPHROTIC SYNDROME:

## Primary kidney diseases :

### C. Membranous nephropathy (glomerulonephritis)



-The common cause of nephrotic syndrome in adult .

-Autoimmune disease (immune complex deposition in GBM)

**- Causes of membranous glomerulonephritis:**

1- infection (Hepatitis B and C ,Syphilis , Schistosomiasis "bilharziasis" and Malaria)

2- Certain drugs (Captopril - NSAIDS- Penicillamine)

3- Exposure to inorganic salt (Gold salt, mercury)

4- SLE

*Sometime immune-complex inside glomerulus acts against phospholipase $A_2$ receptor which found within podocyte

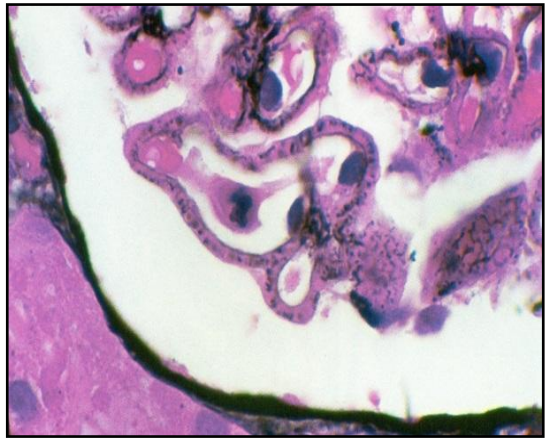
# CAUSES OF NEPHROTIC SYNDROME:

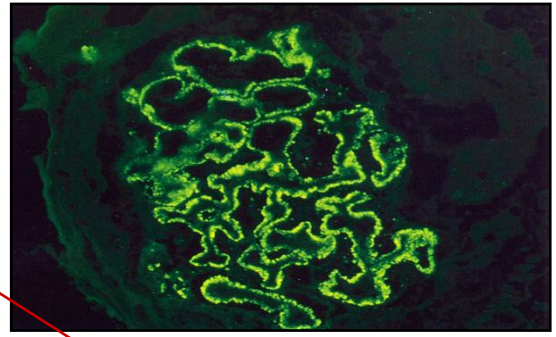
## Primary kidney diseases :

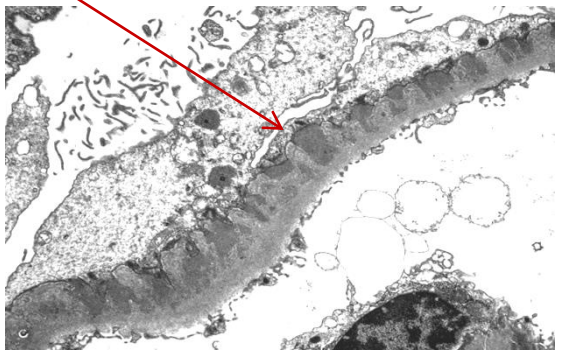
### C. Membranous nephropathy

- L.M: No evident of proliferation + diffuse thickening of capillary walls + global subepithelial deposits may be visualized.
- Silver stain: glomerular basement membrane (spike)
- IF: Distributed granular capillary loop pattern + IgG deposition.
- EM: "spikes" from the basement membrane extended toward the epithelial cells.
- Prognosis:

  Little response to corticosteroid







- Spikes = IgG + complement deposition (C3)

N.B: in LM with silver stain, black color represents GBM but in EM the black color represents spikes.

# CAUSES OF NEPHROTIC SYNDROME:

## Systemic diseases :

### A. Diabetic nephropathy

- Caused by diabetes mellitus (uncontrolled – affected for many years).

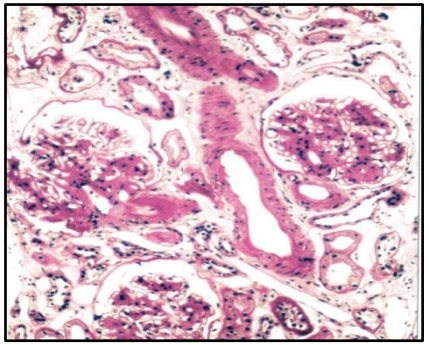
*Global and diffuse glomerulsclerosis can cause renal failure as secondary to DM .

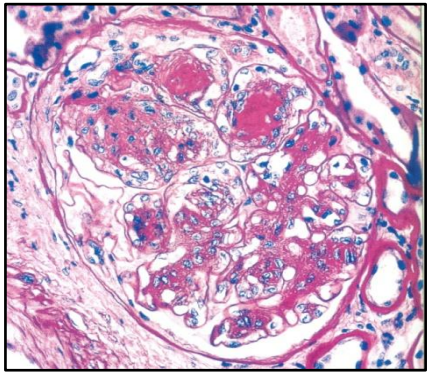
- L.M:

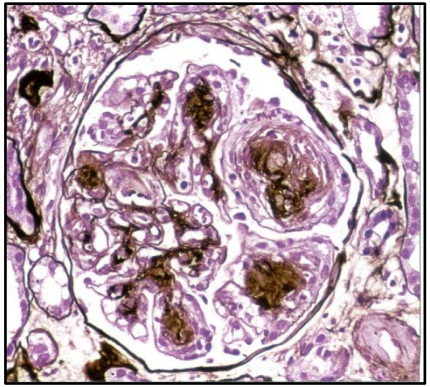
1. Mesangial matrix expansion (pic 1)
2. **Or** with the lamellated appearance of the **Kimmelstiel-Wilson nodule** characteristic of the nodular sclerosis nodular (pic 2).
3. Arteriolar hyalinization. (detect the disease)
4. Tubulointerstitial fibrosis.

- EM: Glomerular basement thickening.

* Diabetic nephropathy usually associated with diabetic retinopathy (eyes abnormalities).



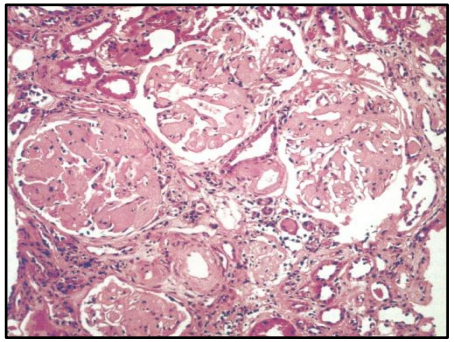




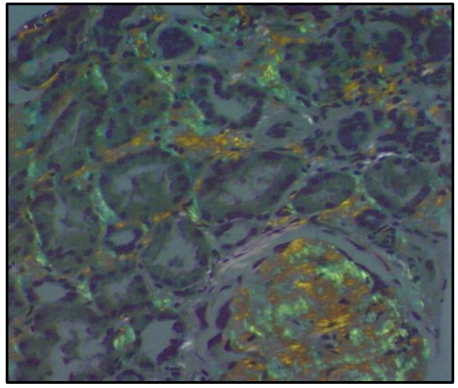
# CAUSES OF NEPHROTIC SYNDROME:

## Systemic diseases :

### B. Renal Amyloidosis



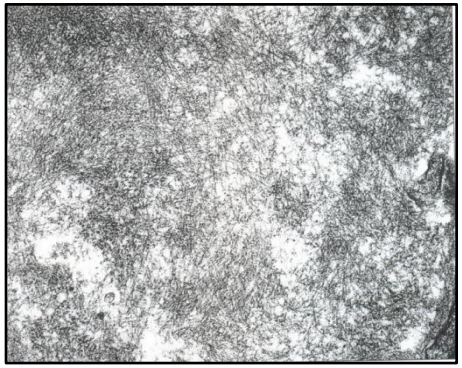
• Usually with patient have chronic bronchitis, TB and osteomyelitis (chronic inflammation condition)



• L.M: Massive amyloid deposits are present in glomeruli and arterioles “hyalinization of blood vessels “-.

• Polarized light with Special stain of amyloid (Congo Red): tubular involvement with amyloid is verified by apple-green birefringence. (pic 2)

• EM: Randomly oriented, typical of amyloid within the **mesangium**.



-Amyloid protein have two types :

1- Amyloid L: light chain: accumulation light Globulin by increasing production of immune-Globulin, Because tumor (ex: multiple myeloma) can affect plasma cell which secrete immune-Globulin.

2- Amyloid AA: Serum amyloid A protein (SAA) is an acute-phase reactant that is deposited

# CAUSES OF NEPHROTIC SYNDROME:

## Systemic diseases :

### C. Systemic lupus erythematosus (class V)

SLE Class V gives secondary membranous nephropathy that leads to nephropathy.

- Auto immune and systemic disease

- It can affect any part in body because antibodies act against DNA.

- These antibodies accumulate in subendothieal.

* U may see spikes, increase mesengial matrix and thickening of peripheral capillary.

## 2. Nephritic syndrome

The diseases that cause nephritic syndrome have in common proliferation cells within the glomeruli, accompanied with inflammatory reaction. The inflammation leads to sever injure to the capillary which allows blood to pass into urine and decreases GFR.

**- Clinical findings:**

1. Hematuria:

- dysmorphic RBCs + Red cells cast
- Smoky brown color (Pepsi-Cola color)

2. Oliguria and Azotemia.*
3. Hypertension:

Due to fluid retention and renin release .

4. Mild edema and Proteinuria *

**- Causes of nephritic syndrome:**

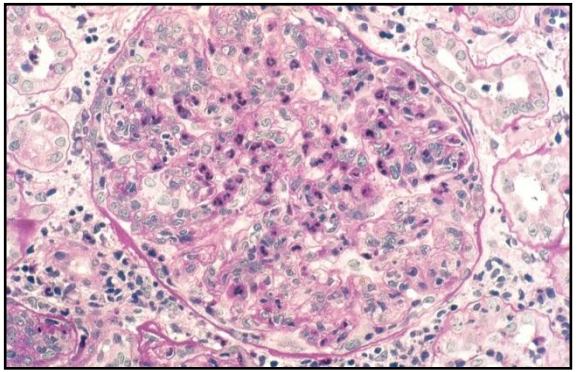
1) Systemic diseases. ( e.g. SLE)
2) Secondary to primary glomerular diseases. (e.g. acute post infectious GN)

*due to decrease in GFR.

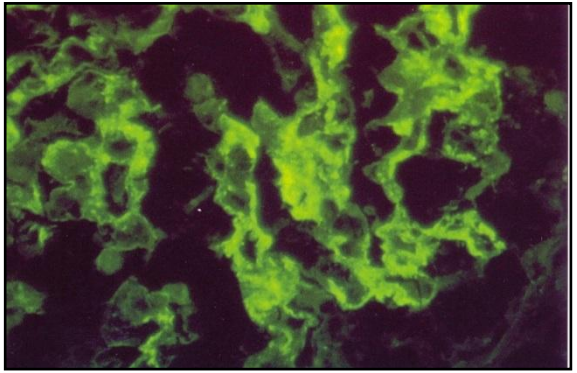
* Not sever as nephrotic syndrome

# CAUSES OF NEPHRITIC SYNDROME:

## 1- Acute proliferative GN OR (poststreptococcal GN) OR (diffuse proliferative GN):



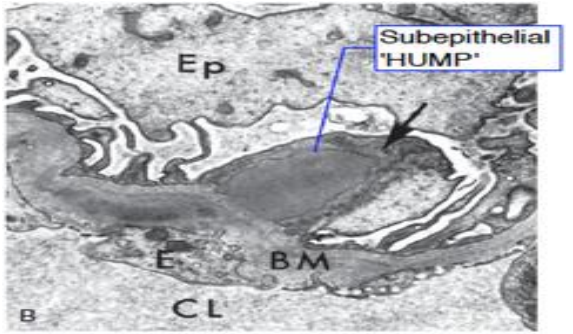
- Glomerular deposition of Immune complex.
- Develops after 1-4 weeks from throat (tonsillitis, pharyngitis) or skin infection with **nephritogenic strains of group A Beta-hemolytic streptococci.**
- L.M: An intense inflammatory reaction involving almost all glomeruli result in:



❑ Hypercellular, proliferation of mesangial and endothelial cells.

❑ Lots of **neutrophils and monocyte** in glomerulus.

- IF : Scattered **granular deposits** of IgG and C3 Within the capillary walls and some mesangial areas (lumpy bumpy appearance )
- EM: Subepithelial **humps**




- Laboratory examinations:
- Anti-Streptolysin-O will be increased
- C3 will be decreased
- Prognosis:

Complete recovery in children, but some of them develop rapidly progressive crescentic GN or chronic renal disease

In Adult depends on severity (worse than children )

# CAUSES OF NEPHRITIC SYNDROME:

## 2- Rapidly progressive (crescentic) GN/Aggressive proliferative glomerunephritis

It's a clinical features of nephritic syndrome + rapid loss of renal function.

Crescents (fibrin and exudates) in bowman capsule, lead to proliferation of parietal epithelial cells, and monocytes

**- Types:**

**A. Anti GBM antibody disease:**

• In some patients, the anti GBM antibodies also bind to pulmonary alveolar capillary basement membrane to produce the clinical picture of pulmonary hemorrhages associated with renal failure. These patient are said to have ''*Goodpasture syndrome*''

•The crescent consists of parietal epithelial cells with some inflammatory cells

•**IF: Linear** deposition of IgG & C3 along the GMB (not granular).

**B. Immune complex mediated:**

Complication of any immune complex like

- Post streptococcal GN.
- SLE.
- IgA nephropathy.
- Henoch-Schonlein purpura.

• **IF: granular** deposition

**C. Wagener granulomatosis / Microscopic polyangitis:**

-Also called **Pauci-immune GN***

-Is immune mediated

-A type of vasculitis (Fibrinoid segmental necrosis)

-There are no immune complexes

-Positive Anti-neutrophil cytoplasmic antibodies (ANCA) in serum .

-Nothing appears in IF and L.M.

*That means lack of anti GBM antibody

# CAUSES OF NEPHRITIC SYNDROME:

## 3- Membranoproliferative glomerulonephritis (MPGN):

- Can presents with nephrotic (most common) or nephritic syndrome
- There is endocapillary proliferation and GMB splitting, due to mesangial and subendothelial deposits, with resultant interposition and new basement membrane being laid down, causing the split appearance.

- **Types:**

**- MPGN type I.**

- L.M: Diffuse endocapillary proliferation, which results in a **lobular**, uniform appearance of glomeruli.
- expansion of mesangial cells lead to split the basement membrane into two layers **(tram track مسار القطار appearance)***
- immune complexes deposited in subendothelial part
- **IF:** IgG and C3
- More common than type II (80% of cases)
- CAUSES:
  A. Hepatitis B and C
  B. SLE
  C. Certain chronic infection

**-Type II: Dense Deposit Disease (DDD)**

Main deposit is complement (complement dysregulation)

**Pathogenesis:**

Inhibition of C3 convertase enzyme, lead to accumulation of C3 by alternative pathway and deposited in the basement membrane.

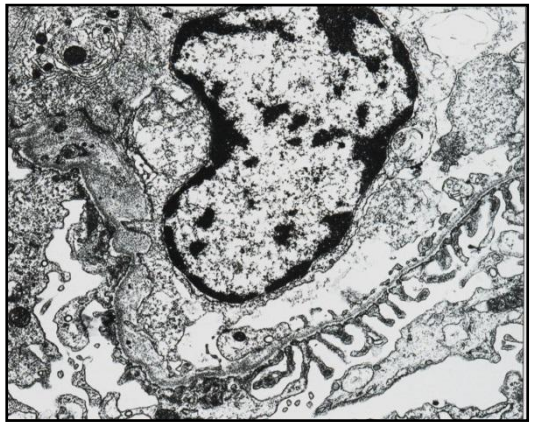
**Prognosis :**

Develop end stage renal disease (ESRD)

*Silver stain showed ''tram track appearance''

# CAUSES OF NEPHRITIC SYNDROME:

## 4- Hereditary nephritis (Alport syndrome):



- Usually affects males (although it's on X chromosome)
- Pathogenesis:

caused by mutations in gene encoding for α-3,α-4 and α-5 chain in collagen IV,

collagen IV constitutes basement membrane, so leads to abnormalities in GBM.

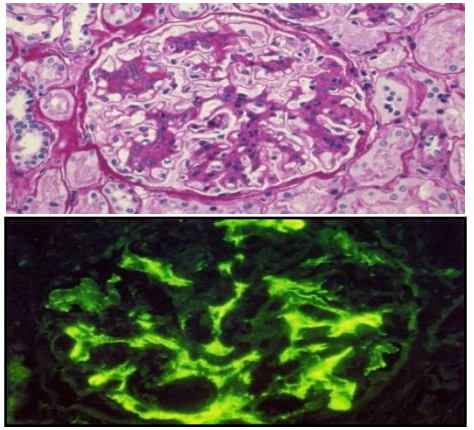
- Clinical findings:

-Nephritis findings

-Eye disorders

- EM: Irregular extreme thinning of glomerular basement membrane and areas of discontinuity.

## 5-IgA nephropathy (Berger disease):



Patient will present with hematuria.

- L.M: Mesangial widening.
- IF: deposition of IgA within mesangium.
- EM: dense deposition of IgA within mesangium and it may extended to subendothelial.

- **Henoch-schonlein purpura (HSP):**

A systemic syndrome involving skin, GIT, joints, and kidney.

Characterized by IgA deposition

## 5. Chronic kidney disease(End- stage kidney disease) :

Result of progression scaring from any type of kidney disease . Patient presents chronic uremia

# SUMMARY *

## SUMMARY: The Nephrotic Syndrome

- The nephrotic syndrome is characterized by proteinuria, which results in hypoalbuminemia and edema.
- Podocyte injury is an underlying mechanism of proteinuria, and may be the result of nonimmune causes (as in minimal-change disease and FSGS) or immune mechanisms (as in membranous nephropathy).
- Minimal-change disease is the most frequent cause of nephrotic syndrome in children; it is manifested by proteinuria and effacement of glomerular foot processes without antibody deposits; the pathogenesis is unknown; the disease responds well to steroid therapy.
- FSGS may be primary (podocyte injury by unknown mechanisms) or secondary (e.g., as a consequence of previous glomerulonephritis, hypertension, or infection such as with HIV); glomeruli show focal and segmental obliteration of capillary lumina, and loss of foot processes; the disease often is resistant to therapy and may progress to end-stage renal disease.
- Membranous nephropathy is caused by an autoimmune response, most often directed against the phospholipase $A_2$ receptor on podocytes; it is characterized by granular subepithelial deposits of antibodies with GBM thickening and loss of foot processes but little or no inflammation; the disease often is resistant to steroid therapy.
- MPGN and dense deposit disease are now recognized to be distinct entities. MPGN is caused by immune complex deposition; dense deposit disease is a consequence of complement dysregulation. Both may present with nephrotic and/or nephritic features.

## SUMMARY: The Nephritic Syndrome

- The nephritic syndrome is characterized by hematuria, oliguria with azotemia, proteinuria, and hypertension.
- The most common cause is immunologically mediated glomerular injury; lesions are characterized by proliferative changes and leukocyte infiltration.
- Acute postinfectious glomerulonephritis typically occurs after streptococcal infection in children and young adults but may occur following infection with many other organisms; it is caused by deposition of immune complexes, mainly in the subepithelial spaces, with abundant neutrophils and proliferation of glomerular cells. Most affected children recover; the prognosis is worse in adults.
- IgA nephropathy, characterized by mesangial deposits of IgA-containing immune complexes, is the most common cause of the nephritic syndrome worldwide; it is also a common cause of recurrent hematuria; it commonly affects children and young adults and has a variable course.
- Hereditary nephritis (Alport syndrome) is caused by mutations in genes encoding GBM collagen; it manifests as hematuria and slowly progressing proteinuria and declining renal function; glomeruli appear normal by light microscopy until late in the disease course.

## SUMMARY: Rapidly Progressive Glomerulonephritis (RPGN)

- RPGN is a clinical entity with features of the nephritic syndrome and rapid loss of renal function.
- RPGN is commonly associated with severe glomerular injury with necrosis and GBM breaks and subsequent proliferation of parietal epithelium (crescents).
- RPGN may be immune-mediated, as when autoantibodies to the GBM develop in anti-GBM antibody disease or when it arises consequent to immune complex deposition; it also can be pauci-immune, associated with antineutrophil cytoplasmic antibodies.

* From Robbins

# MCQs

1- A patient has a lot of protein in the urine > 3 g/24h Causing hypoalbuminemia which leads to edematous patient, what does he have?

A. Nephrotic syndrome

B. Nephritic syndrome

C. Tumor

D. Asymptomatic hematuria/proteinuria

2- Which of the following is a systemic disease which cause the nephrotic syndrome?

A. MINIMAL CHANGE DISEASE

B. Focal segmental glomerulosclerosis

C. Membranous glomerulopathy

D. Lupus membranous glomerulopathy

3- How can you detect the abnormalities in “minimal change” disease?

A. Using electron microscope

B. Using immunofluorescence test

C. using light microscope

D. using light microscope with special stain

Answer :
1- A
2- D
3- A

# MCQs

4- What do we call the abnormal architecture in Focal segmental glomerulonephritis of the glomeruli, capillaries, adhesion of bowman's capsule?

A. Glomerulonecrosis

B. Glomerulosclerosis

C. Both

D. Either

5- Where does the immunocomplex deposit in the Membranous nephropathy in immunofluorescence test?

A. Bowman's space

B. Mesangium

C. Capillaries

D. Arterioles

6- What does the spikes do?

A. Injured basement membrane

B. Causing Areas of necrosis

C. Both

D. Neither

Answer :
4- B
5- C
6- A

# MCQs

7- An old patient came with edema in his leg , his abdomen is dilated, he was feeling weakness and sleepy , examination shows presence of protein in urine (proteinuria). Which of the following syndrome does the patient has?

A. Rapidly progressive GN

B. Nephrotic syndrome

C. Nephritic syndrome

D. Chronic renal failure

8- Which one of the following diseases is most often treated by corticosteroid?

A. Minimal change disease

B. Focal segmental glomerulosclerosis

C. Membranous glomerulonephritis

D. Renal amyloidosis

9- Which proteins in nephrotic syndrome mostly loss with urine?

A. Low-weight proteins.

B. High weight proteins.

C. Albumin.

D. A & C

Answer :
7- B
8- A
9-D

# MCQs

10- In which disease the basement membrane become changes?

A. Minimal change disease
B. Focal segmental glomerulosclerosis
C. Membranous glomerulonephritis
D. Renal amyloidosis

11- In which disease the Immune complex deposition in subendothelial location?

A. Lupus nephropathy
B. Diabetic nephropathy
C. Focal segmental glomerulosclerosis
D. Renal amyloidosis

12- What is the major primary cause of the nephrotic syndrome?

A. Membranous glomerulonephritis
B. Diabetic nephropathy
C. Renal amyloidosis
D. Lupus nephropathy

Answer :
10- C
11-A
12-A

# MCQs

13- In which disorders will have Tram-track appearance?

A. Alport syndrome
B. Goodpasture syndrome
C. IgA nephropathy
D. Membranoproliferative glomerulonephritis

14- One of the clinical findings in nephritic syndrome is?

A. Severe pitting edema
B. Lipiduria
C. Red cell casts (Smoky brownish urine )
D. Hypotension

15- The prognosis of post streptococcal GN are?

A. Bad and often progresses to end stage renal disease
B. Very good with complete recovery in all children and many adults
C. Very bad because of sever glomerular damage but better in adults

16- In Immunofluorescence of post streptococcal GN case we can see?

A. IgG and C3 deposition in subepithelial mesangial areas (lumpy bumpy )
B. Linear depositions of IgG and C3
C. IgA antibodies deposition in the wall of glomerular capillaries
D. Immune complexes deposition in spike and dome appearance

17- The gene responsible for Alport syndrome is?

A. On the Y chromosome
B. Encodes for (α-5) protein chain
C. Is responsible for the formation of collagen type II
D. On chromosome 22

Answer :
13-D
14-C
15-B
16-A
17-B

# MCQs

18- Alport syndrome is more common in?

A. Postmenopausal woman
B. Males from 40-60 years old
C. Children (males)
D. Young adults

19- In rapidly progressive GN we can see?

A. Proliferation of the meningeal cells
B. Splitting of the basement membrane
C. Effacement of the podocyts processes
D. Proliferation of parietal epithelial cells of bowman's capsule

20- Clinical manifestations of Goodpasture syndrome include?

A. Nephrotic syndrome
B. Pneumonitis with hemoptysis
C. Berger disease
D. Vasculitis

21- The most common cause of nephritis is?

A. IgA nephropathy
B. Alport syndrome
C. Membranoproliferative GN
D. Wagener granulomatosis

Answer :
18-C
19-D
20-B
21-A

# Team Member's

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