REVISE NEPHROLOGY

NEPHROTIC SYNDROME

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LEARNING OBJECTIVES

- Definition and D/D of nephrotic syndrome
- Basic pathological and clinical differences between:
  - MCD: Foot process effacement **(No GBM or mesangial involvement)**
  - FSGS: Sclerosis with foot process effacement **(No GBM or mesangial involvement)**
  - MN: Thickened GBM with sub-epithelial deposits **(No mesangial involvement)**
  - MPGN/MCGN: **Mesangial and endocapillary cellular proliferation** along with **mesangial and subendothelial deposits** (occ. subepithelial deposits too) and **thickened GBM with double-contour (tram track**) appearance
  - General management of nephrotic syndrome with targeted therapy for the above 4 entities

WHEN DO I CALL IT NEPHROTIC SYNDROME……

- **Proteinuria>3.5g/day**
- **Hypoalbuminemia**
- **Oedema**

Frequently observed:

- Hyperlipidaemia
- Hypercoagulability and thrombotic events (8 times more likelihood of arterial and venous thrombosis; more in membranous nephropathy)

DIFFERENTIAL DIAGNOSIS OF NEPHROTIC SYNDROME

Primarily Glomerular pathology

- Minimum Change Disease (MCD)
- Focal Segmental Glomerulosclerosis (FSGS)
- Membranous Nephropathy (MN)
- Membranoproliferative (MPGN)/Mesangiocapillary (MCGN)- is least common AND can be nephrotic or nephritis

Systemic diseases (30% in adults)

- Diabetes Mellitus
- Amyloidosis
- Lupus (usually causes membranous nephropathy)

Heavy proteinuria without oedema or hypoalbuminemia is more likely to be due to secondary FSGS ,e.g., to diabetes

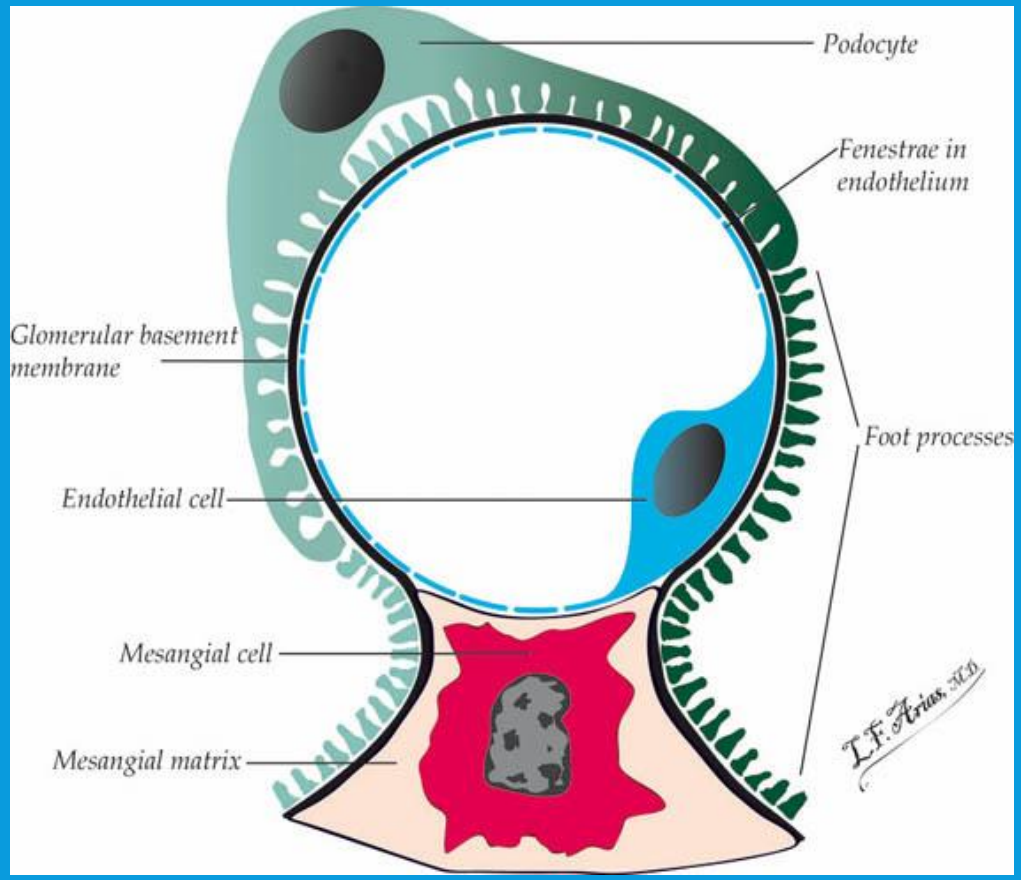
PROTEIN LOSS

Defect in the glomerular filtration barrier

- Endothelial gap- 50 to 100nm
- Filtration slit with a width of 30 to 40nm bridged by slit diaphragm
- with 8 nm sized pores

NEGATIVE CHARGES ALL OVER THE FILTRATION BARRIER

* **Size of albumin- 7.2 nm**



KIDNEY INJURY IN NS

- **AKI is not very common and may be due to**
  - Hypovolemia due to aggressive diuresis
  - ATN (most commonly seen in MCD)
  - Interstitial nephritis from diuretics
  - Intrarenal edema leading to compression of tubules
  - Rarely bilateral renal vein thrombosis
- **CKD is common**
  - Apart from MCD, most cases of NS have risk of CKD
  - Risk of progression increases with degree of proteinuria

QUICK REVIEW OF DIFFERENT GLOMERULAR PATHOLOGIES IN NEPHROTIC SYNDROME

1.MCD: **Foot process effacement** on EM (normal LM and IF)

2. FSGS: LM shows **sclerosis** in parts (segmental) of some (focal) glomeruli with EM showing **foot process effacement** (normal IF)

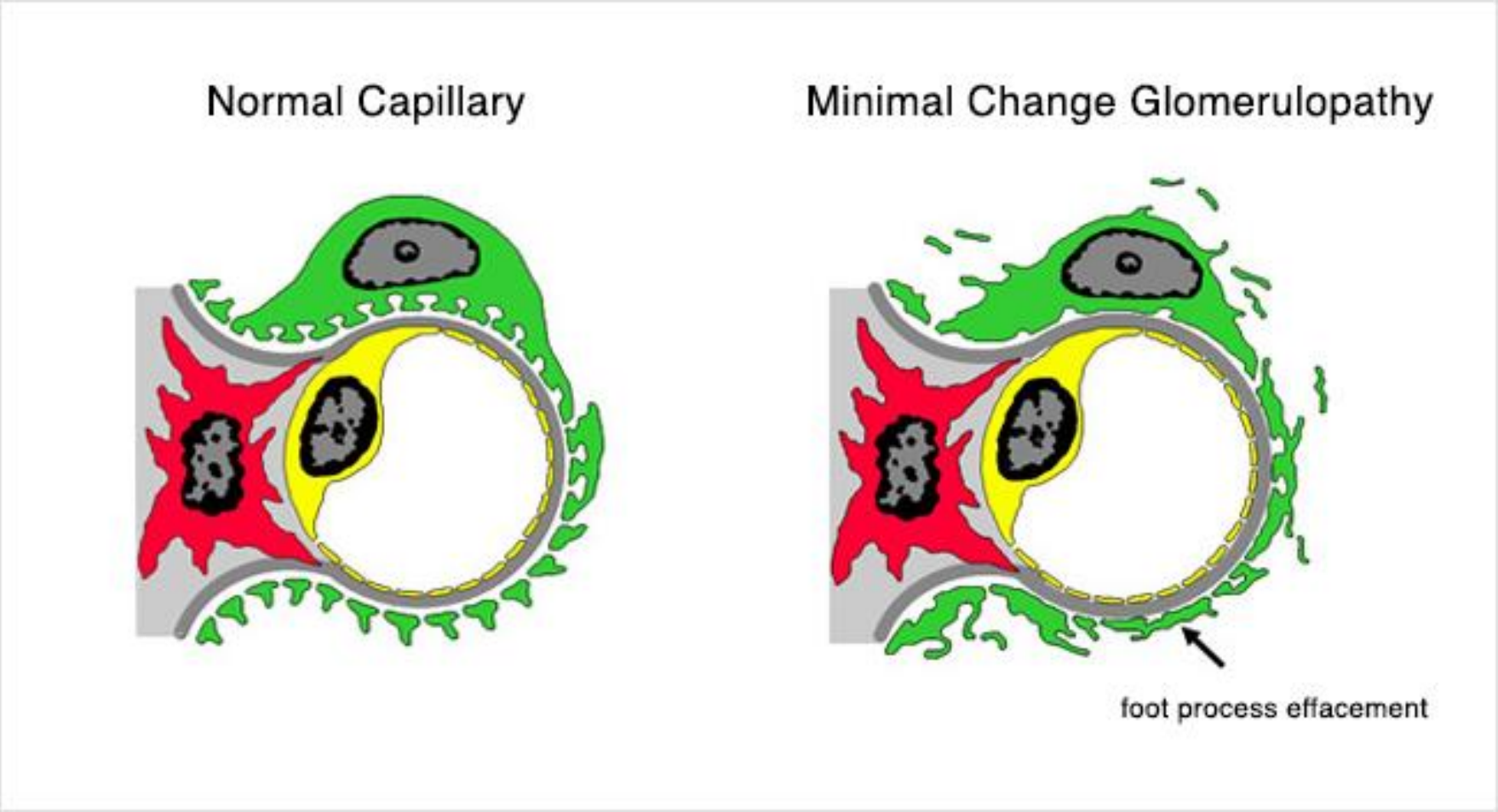
3. MN: **Thickened GBM with no cellular proliferation on** LM ; EM show **sub-epithelial deposits** (spikes and domes with thickened GBM) and IF shows IgG

- *MESANGIUM is characteristically normal and no sub-endothelial deposits*

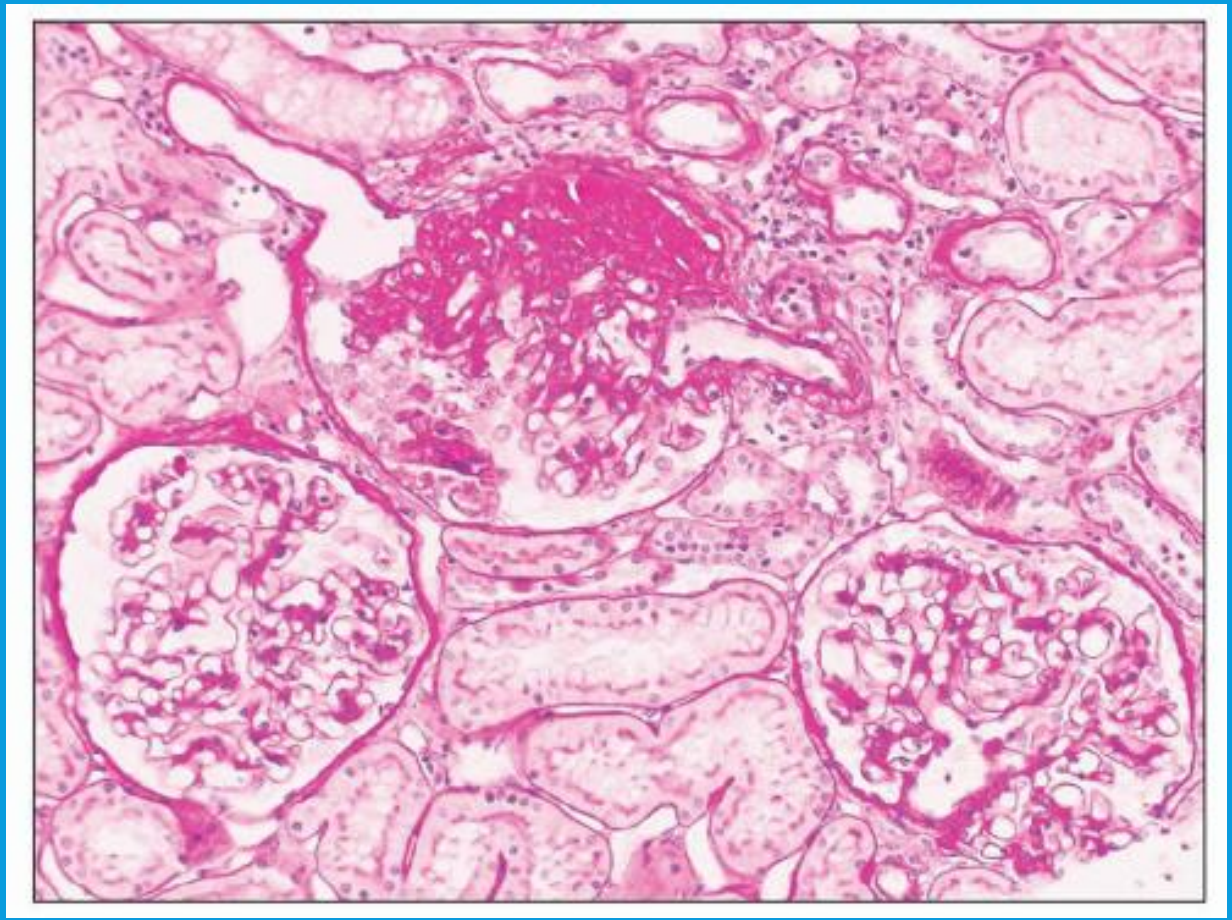
4. MCGN (MPGN): **Mesangial and endocapillary cellular proliferation** (*manifests as difficult to visualise capillaries as full of cells*)) **with thickened GBM leading to a double-contour** (tram track) appearance of glomerular capillary walls

- EM may show **both subepithelial and subendothelial deposits**
- IF may show Ig or only C depending on the type (immune vs complement-mediated MCGN)

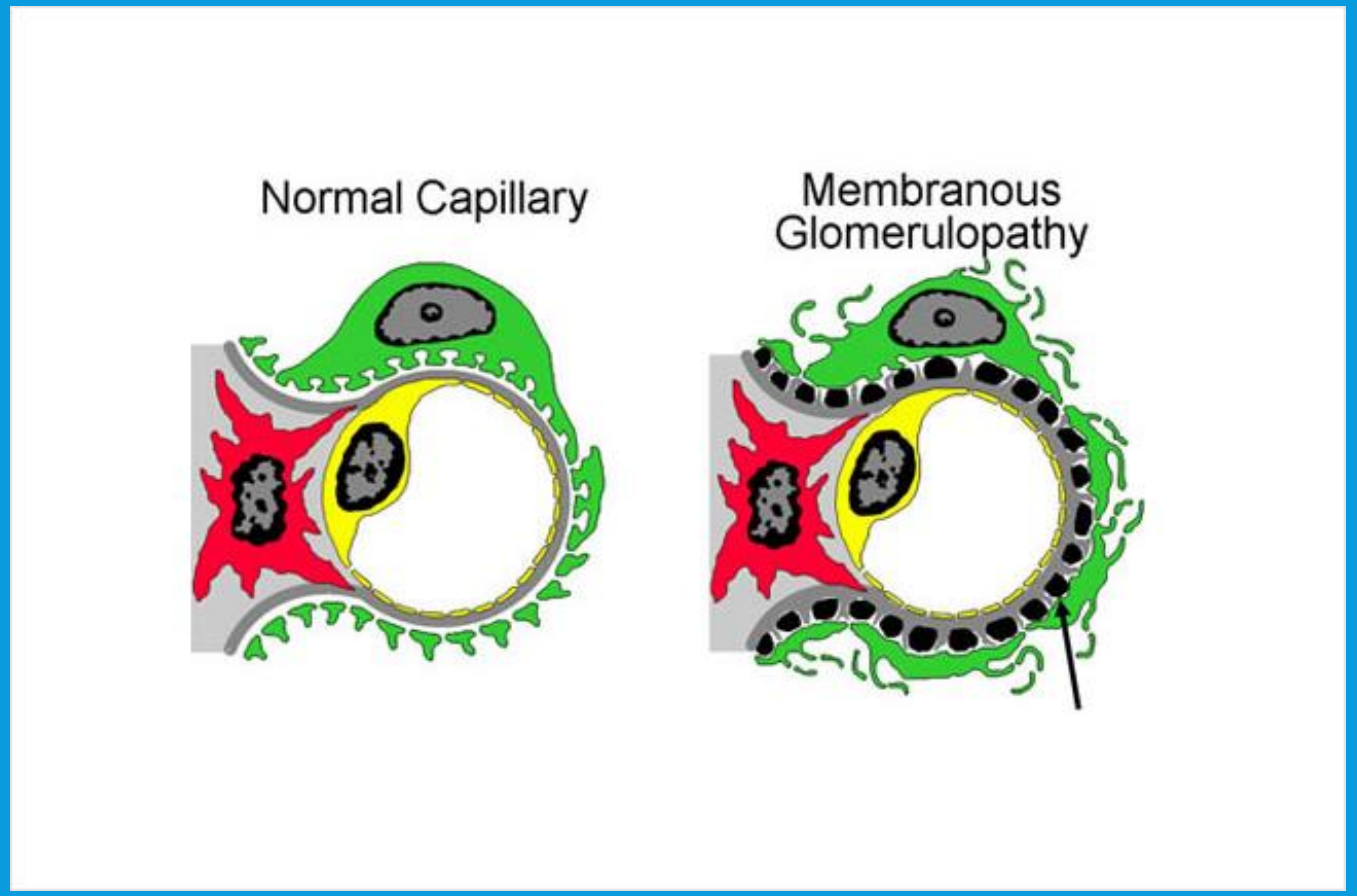
NORMAL VS MCD



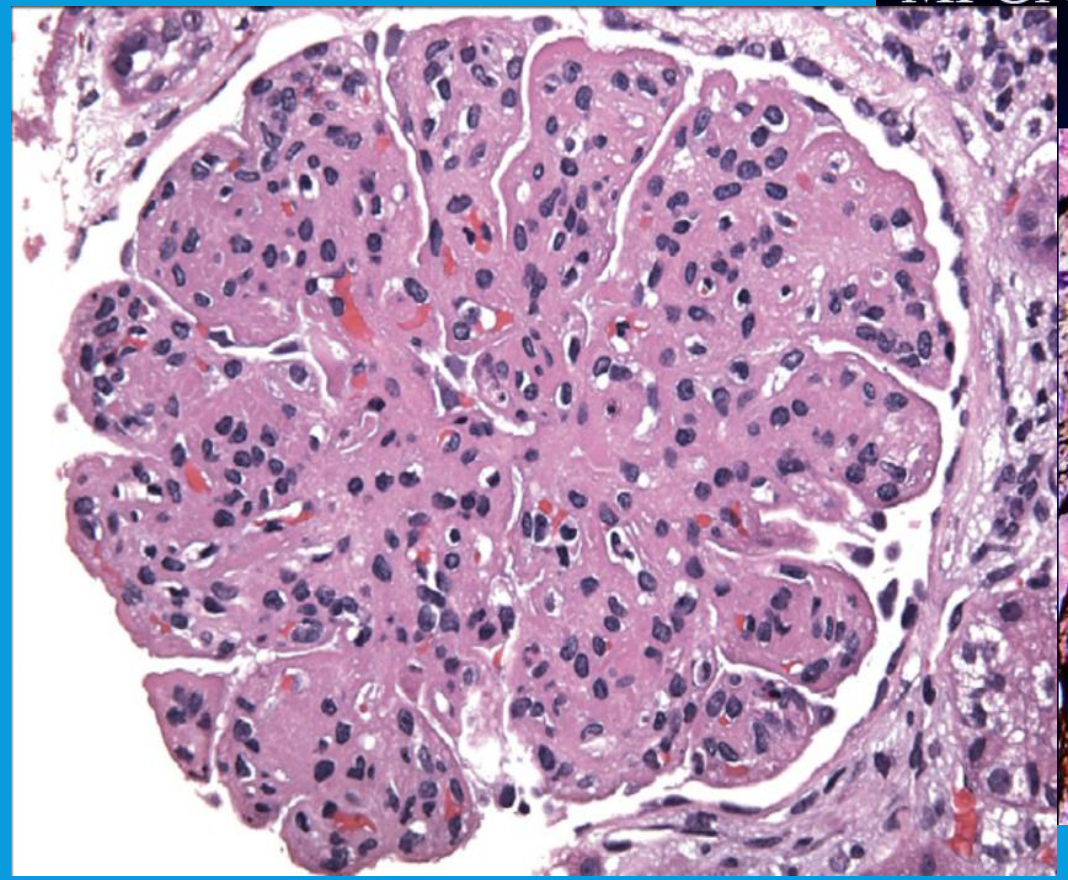
FSGS

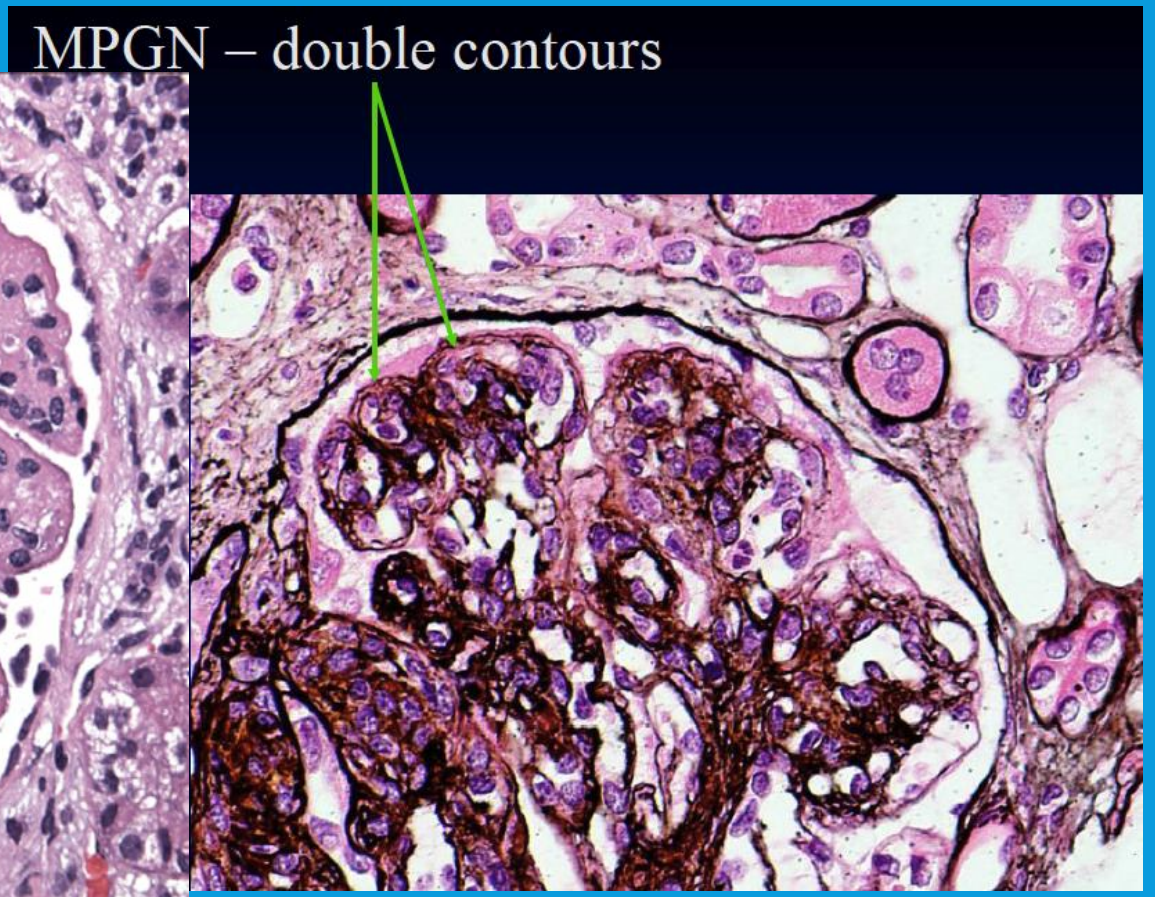


MEMBRANOUS NEPHROPATHY (THICK GBM WITH SUB-EPITHELIAL DEPOSITS CAUSING SPIKES WITH NO MESANGIAL OR SUB-ENDOTHELIAL DEPOSITS)



MCGN (MESANGIAL AND ENDOTHELIAL HYPERCELLULARITY CAUSING OBLITERATION OF CAPILLARIES AND DOUBLE CONTOUR/TRAM TRACK APPEARANCE)

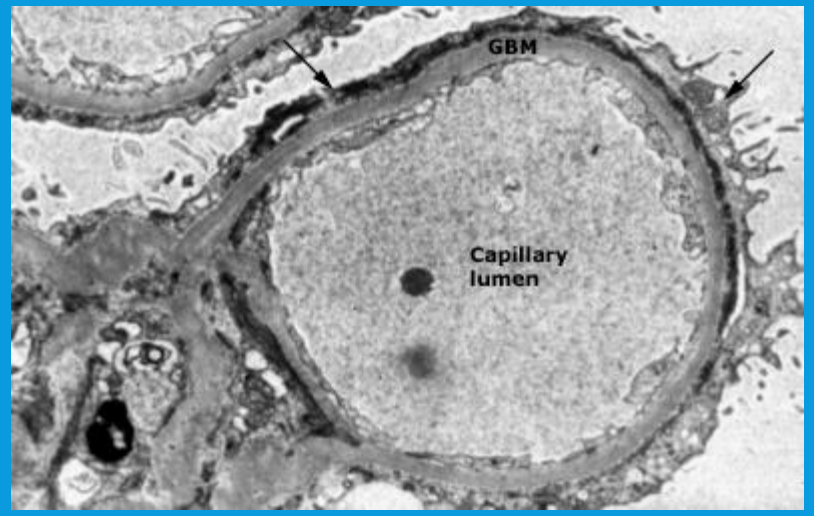




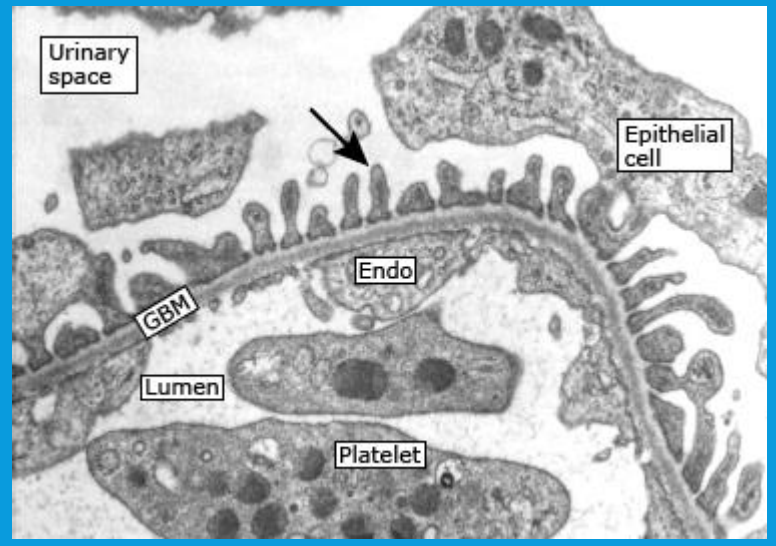
MINIMAL CHANGE DISEASE (MCD)

- Cause of nephrotic syndrome in>90% children below 10 years
- Among adults: more acute and more likely to present with AKI
- LM and IF- normal; EM- effacement of podocyte foot processes

Pic- Foot process fusion/effacement



Pic- Normal glomeruli



MCD….. MOSTLY UNKNOWN AETIOLOGY

- **Onset and progress of nephrotic syndrome usually faster than other glomerular pathologies (days to week or two)**

  Association-

  - Drugs- **NSAIDs**, Interferon-alpha, antibiotics (ampicillin, rifampicin, cephalosporins),pamidronate, lithium
  - Neoplasm- **Hodgkin lymphoma** and less commonly non-Hodgkin lymphoma and leukemia
  - Allergy- atopy/asthma/eczema history in up to 30%

MCD VERSUS PRIMARY FSGS

- Primary MCD versus primary FSGS- ??variants of same disease
  - Both have foot process effacement
  - Both response to corticosteroids

But wait…..SUPAR association in primary FSGS but not MCD

……..CD8o overexpression on podocytes in MCD but not FSGS

PATHOGENESIS

- Primarily podocyte abnormality
- Involvement of cell mediated immunity
  - Activated T cells secrete increased IL-13
  - IL-13 leads to CD80 expression on podocytes
  - CD80 leads to decreased expression of nephrin
  - **Nephrin is the major negative protein on the filtration barrier**
- Glucocorticoids and cyclophosphamide which modify cell-mediated responses, have proven benefit in the treatment of MCD

TREATMENT AND PROGNOSIS

- AKI uncommon in children but commoner in adults
- Low Na diet and diuretics
- Statins
- **Good response to corticosteroids**
- Multiple relapses usually seen and generally respond to steroids
- Second line therapy for frequent relapses and corticosteroid dependent- cyclophosphamide/cyclosporine or tacrolimus (CNIs)
- Rituximab for those who failed all of above

Beware-relapses more common with CNI and may need long term continuation

MEMBRANOUS NEPHROPATHY (MN)

- Commonest glomerular cause of NS in adult Caucasians
- GBM thickening with no cellular proliferation or infiltration
- Immune deposits beneath podocytes (subepithelial)/**No hypercellularity/No mesangial involvement**
- 1/3rd cases are associated with following conditions (2/3rd primary or idiopathic)
  - Connective tissue disease: **SLE (commonest),** rheumatoid arthritis
  - Infections: **Hepatitis B(commonest),**Hepatitis C, schistosomiasis, malaria, filariasis
  - Drugs**: Penicillamine**, **NSAIDs, anti-TNF(Infliximab),**gold, captopril

➢ Tumours (specially in >65 years) : **Mostly solid organs malignancies like prostate, lung, or gastrointestinal track**, less often CLL

MN

- Two third cases have no known association- termed primary MN
- Antibody to phospholipase A2 receptor(anti-PLA2R) seen in 70% of primary MN but not in secondary cases
- Up to 24% of patients who do not have circulating PLA2R antibodies have PLA2R antigen detected within glomerular immune deposits by IF
- PLA2R is expressed on the podocytes- hence the subepithelial deposit
- **Anti-PLA2R levels have a strong association with prognosis**
- Thrombospondin type-1 domain-containing 7A (THSD7A) is the podocyte antigen in 10% cases of anti-PLA2R negative (so 3% of all primary MN)

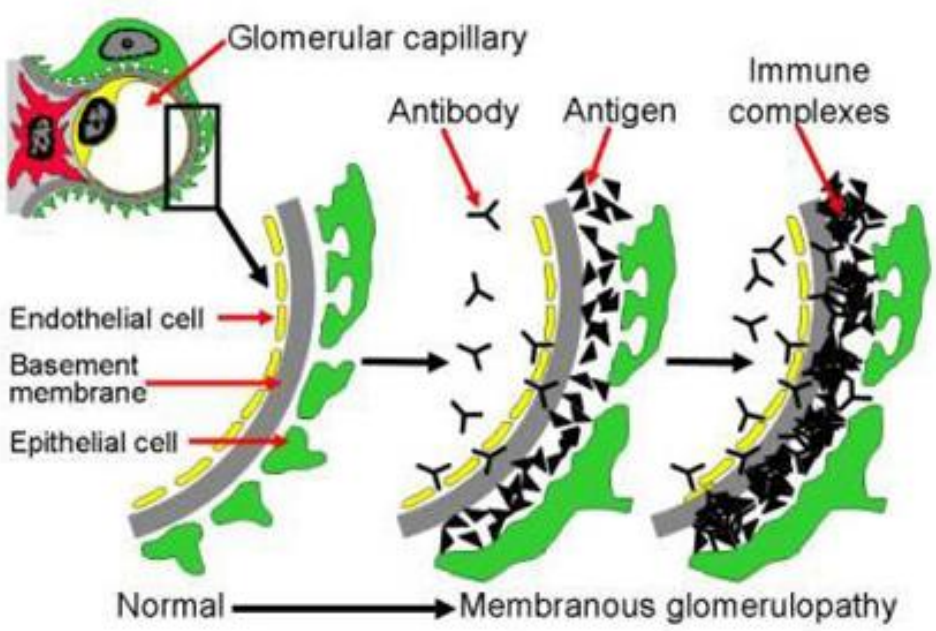
Thrombospondin Type-1 Domain-Containing 7A in Idiopathic Membranous Nephropathy

N Engl J Med 2015; 372:1073-1075March 12, 2015DOI: 10.1056/NEJMc1500130

PATHOGENESIS OF MN

- IgG antibodies pass across GBM to target antigens on podocyte foot process e.g. PLA2R
- Resultant antigen-antibody complex activates complement
- C5-9 enters podocytes and the complement-mediated podocyte injury leads to two changes
  - *Proteinuria via redistribution of actin and loss of slit diaphragm integrity*
  - *GBM expansion by the overproduction of type IV collagen and laminin by the injured podocytes*
- The immune complexes are capped and shed to form subepithelial deposits
- GBM grows around the deposits to form spikes initially and then domes

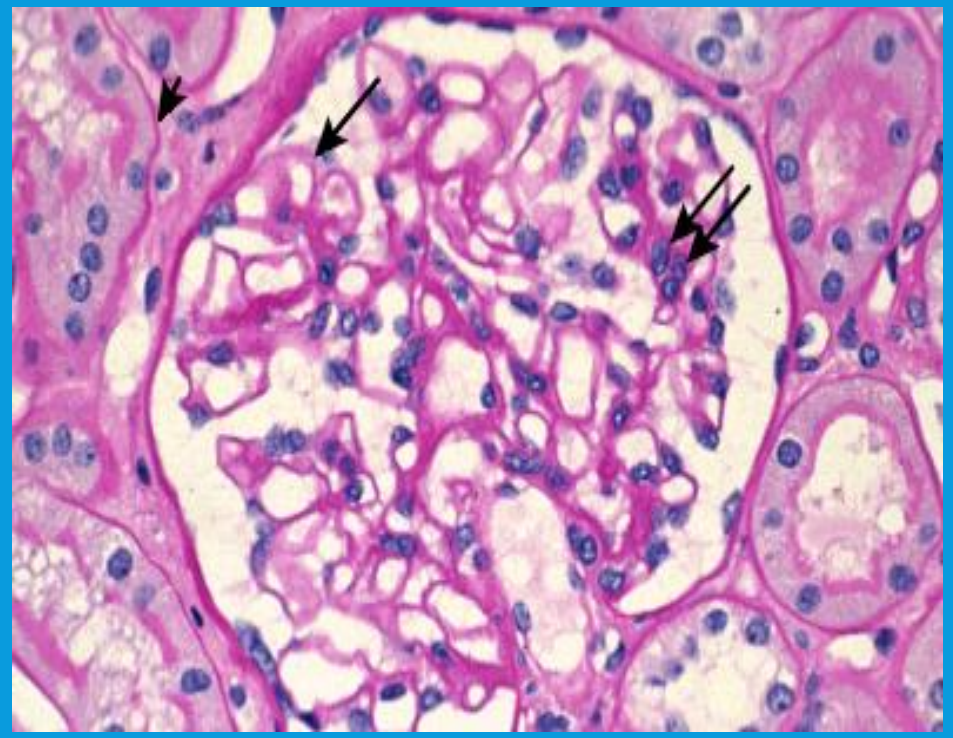
PATHOGENESIS OF MN

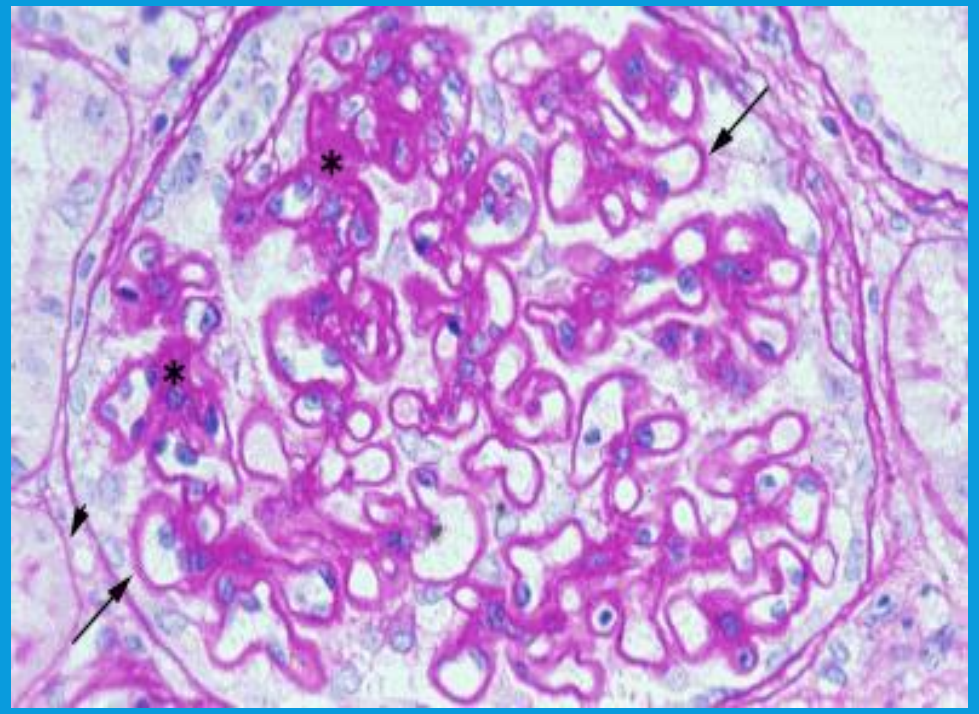


LIGHT MICROSCOPY

NORMAL GLOMERULI- THICKNESS OF GBM (LONG ARROW) IS SIMILAR TO THAT OF THE TUBULAR BASEMENT MEMBRANES (SHORT ARROW)

MN- GBM THICKER (LONG ARROW) COMPARED TO TUBULAR BASEMENT MEMBRANES (SHORT ARROW)

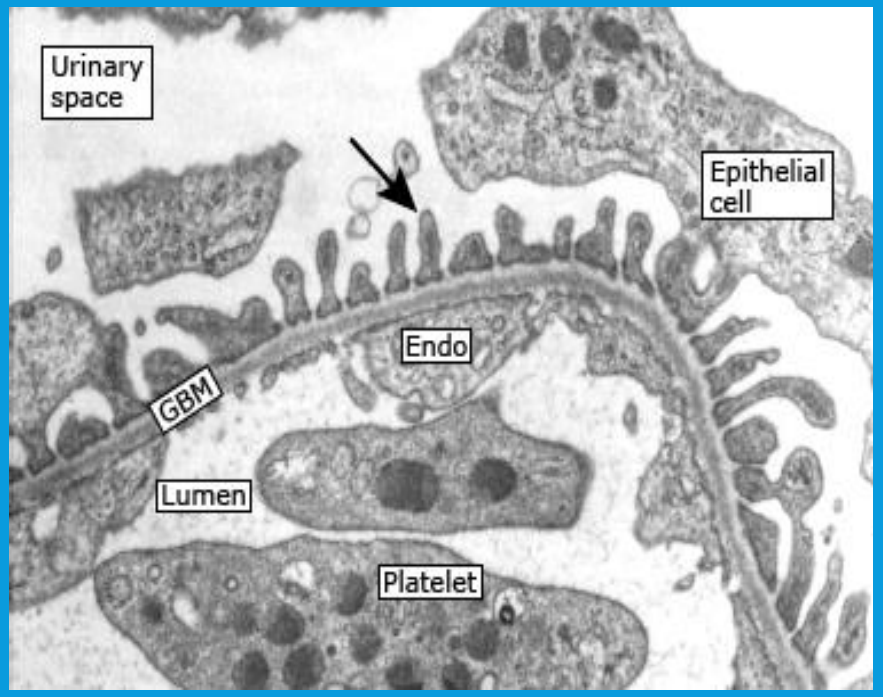


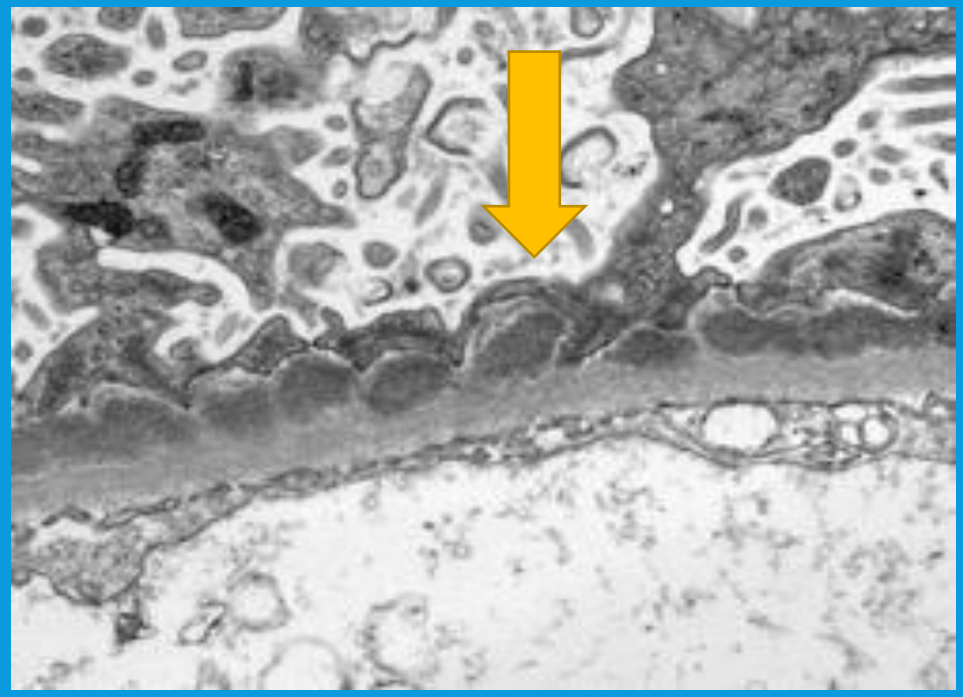


ELECTRON MICROSCOPY

NORMAL GLOMERULI- GBM IS THIN AND NO ELECTRON-DENSE IMMUNE DEPOSITS ARE PRESENT

MN- SUBEPITHELIAL IMMUNE DEPOSITS WITH THE GBM GROWING AROUND THEM AND GETTING THICKENED





PROGNOSIS OF MN (OVER FIVE YEARS)

- Low risk – Proteinuria < 4 g/day and normal creatinine over 6 months: less than 8 % develop CKD
- Moderate risk – Proteinuria between 4 and 8 g/day for > 6 months with normal or near normal creatinine : CKD in 50 %
- High risk – Proteinuria >8 g/day and persists for three months and/or renal function that is either below normal or decreases: CKD in 75 %
- *Serial anti-PLA2R antibody titres are high ≥150 and not declining **or** increasing to ≥150 is independent risk factor for high risk*

A Proposal for a Serology-Based Approach to Membranous Nephropathy, De Vriese AS, Glassock RJ, Nath KA, Sethi S, Fervenza FC J Am Soc Nephrol. 2017;28(2):421; PMID 27777266

	Low	Moderate	High	Very high(any 2 of on diagnosis)
Kidney function	Normal or stable (<25 %decrease) eGFR over 3-6 month period	Normal or stable (<25 %decrease) eGFR over 3-6 month period	Decrease in eGFR of ≥25 percent over 3-6 months	Serum Cr ≥1.5 mg/dL [≥133 micromol/L] **OR** declining eGFR ≥25% in 2 years
Proteinuria	Proteinuria <4 g/day over 3-6 months	Persistently between 4 and 8 g/day over 3-6 months	Proteinuria >8 g/day **or** persistent nephrotic syndrome over 3-6 months	Severe, disabling, or life-threatening NS i.e albumin<20 g/L, severe oedema, thromboembolism
Plasma level of anti-PLA2R antibody in RU/mL (in those positive)	Serial anti-PLA2R antibody titers are low i.e. <50 or decreasing by ≥25% at 3-6 months	Serial anti-PLA2R antibody titres are <150 **and** stable or increasing by <25% over 3-6 months	Serial anti-PLA2R antibody titres are high ≥150 and not declining **or** increasin g to ≥150	

TREATMENT OF MN

- Angiotensin inhibition and BP control, diuresis, lipid lowering, salt restriction(< 2 g/day)
- Treatment of underlying disease in secondary MN
- Prophylactic anti-coagulation if serum albumin< 20g/L and any of the following (cease when albumin> 30g/L):

-Proteinuria>10g/d

-BMI >35kg/m2

-Prior or family history of thromboembolism

-NYHA class III or IV CCF

-Recent abdominal or orthopaedic surgery

-Prolonged immobilization

CHOICE OF IMMUNOSUPPRESSIVE THERAPY

- **Moderate risk of progression:**
  - Stable or progressive increase in proteinuria over 3-6 months offered rituximab
  - If rituximab is unavailable, **either** glucocorticoids plus cyclophosphamide or CNI monotherapy *(cyclosporine or tacrolimus)*
  - In progressive improvement in proteinuria, no immunosuppression indicated
- **Low risk of progression:** general supportive measures (ACEI/ARB, salt restriction etc.) and no immunosuppressive therapy

CHOICE OF IMMUNOSUPPRESSIVE THERAPY

- **High or very high-risk patients:**
  - Cyclophosphamide or prednisolone for those with abnormal kidney function at presentation **or** rapidly declining kidney function
  - Rituximab OR CNI (cyclosporine or tacrolimus) and prednisolone for those with stable kidney function
- Membranous Nephropathy Trial of Rituximab (MENTOR) trial showed for patients with heavy proteinuria but mostly preserved kidney function, rituximab was more effective than cyclosporine at maintaining complete or partial remission of proteinuria at 24 months

Read up: 'Rituximab or Cyclosporine in the Treatment of Membranous Nephropathy'Fernando C. Fervenza et al July 4, 2019; N Engl J Med 2019; 381:36-46; DOI: 10.1056/NEJMoa1814427

FOCAL SEGMENTAL GLOMERULOSCLEROSIS (FSGS)

- A histologic lesion, rather than specific disease entity, defined as sclerosis in parts (segmental) of some (focal) glomeruli
- Commonest cause of NS in adult population of African origin
- The non sclerotic glomeruli in FSGS show foot process effacement….*so are MCD and FSGS two spectrums of a same disease?*
- > 80% are primary (idiopathic) and most in this group have elevated plasma 'soluble urokinase type plasminogen activator receptor' (suPAR)

Table 1. Causes of Focal Segmental Glomerulosclerosis.

Type of Disease	Cause
Primary (idiopathic) form	Specific cause unknown; mediated by circulating permeability factors
Secondary forms	
Familial or genetic	Mutations in specific podocyte genes*
Virus-associated	Human immunodeficiency virus type 1, parvovirus B19, simian virus 40, cytomegalovirus, Epstein–Barr virus
Drug-induced	Heroin; interferons alfa, beta, and gamma; lithium; pamidronate; sirolimus; calcineurin-inhibitor nephrotoxicity; anabolic steroids
Adaptive†	Conditions with reduced renal mass: oligomeganephronia, very low birth weight, unilateral renal agenesis, renal dysplasia, reflux nephropathy, sequela to cortical necrosis, surgical renal ablation, renal allograft, aging kidney, any advanced renal disease with reduced functioning nephrons Conditions with initially normal renal mass: systemic hypertension, acute or chronic vaso-occlusive processes (atheroembolization, thrombotic microangiopathy, renal-artery stenosis), elevated body-mass index (obesity, increased lean body mass [e.g., bodybuilding]), cyanotic congenital heart disease, sickle cell anemia

* For details regarding genetic mutations associated with focal segmental glomerulosclerosis, see the table in the Supplementary Appendix.
† The adaptive form is mediated by adaptive structural–functional responses to glomerular hypertension caused by elevated glomerular capillary pressures and flows.

D'Agati VD et al. N Engl J Med 2011;365:2398-2411.

PATHOGENESIS OF PRIMARY FSGS AND SUPAR

- More than two third of primary FSGS is associated with increased plasma level of suPAR (soluble urokinase Plasminogen Activating Receptor)
- SuPAR leads to increase in alpha-v-b3 integrin activity which in turn leads to foot process effacement and proteinuria
- Increased serum levels of suPAR before renal transplantation associated with an increased risk of recurrent disease in the allograft
- Plasmapheresis after transplantation in recurrent FSGS can lead to decreased suPAR and improvement in proteinuria
- *However, suPAR levels are known to be high in people with low GFR in the absence of primary FSGS*

MIR-193A AND APOL1

- Expression of a specific microRNA called miR-193a can also produce FSGS in mice
- miR-193a inhibits the expression of various genes important for podocyte function including the negatively charged podocyte protein nephrin
- **Polymorphisms in the apolipoprotein L1 (APOL1) gene on chromosome 22 has association with FSGS in people of African origin**
- APOL1 provides innate immunity against trypanosomiasis

APOL1-Associated Nephropathy: A Key Contributor to Racial Disparities in CKD' Barry I. Freedman, Sophie Limou, Lijun Ma, and Jeffrey B. Kopp Am J Kidney Dis. 72(5)(Suppl 1):S8-S16. doi: 10.1053/j.ajkd.2018.06.020

SECONDARY FSGS

- Subnephrotic or nephrotic-range proteinuria with little or no hypoalbuminemia/oedema common in secondary FSGS
- Results from **adaptive response to:**
- ***glomerular hypertrophy/hyperfiltration*** *e.g. diabetic nephropathy*
- ***scarring due to previous injury*** *e.g. lupus nephritis*
- ***reduced renal mass*** *e.g. reflux nephropathy, surgical ablation*
- ***direct toxic injury to podocytes*** *e.g. drugs like heroin, interferon etc.*
- ***virus associated*** *e.g. HIV, parvovirus B19*
- Beware especially in the young that genetic FSGS can present with subnephrotic proteinuria or nephrotic range proteinuria **without** full blown nephrotic syndrome

HISTOLOGICAL CLASSIFICATION OF FSGS

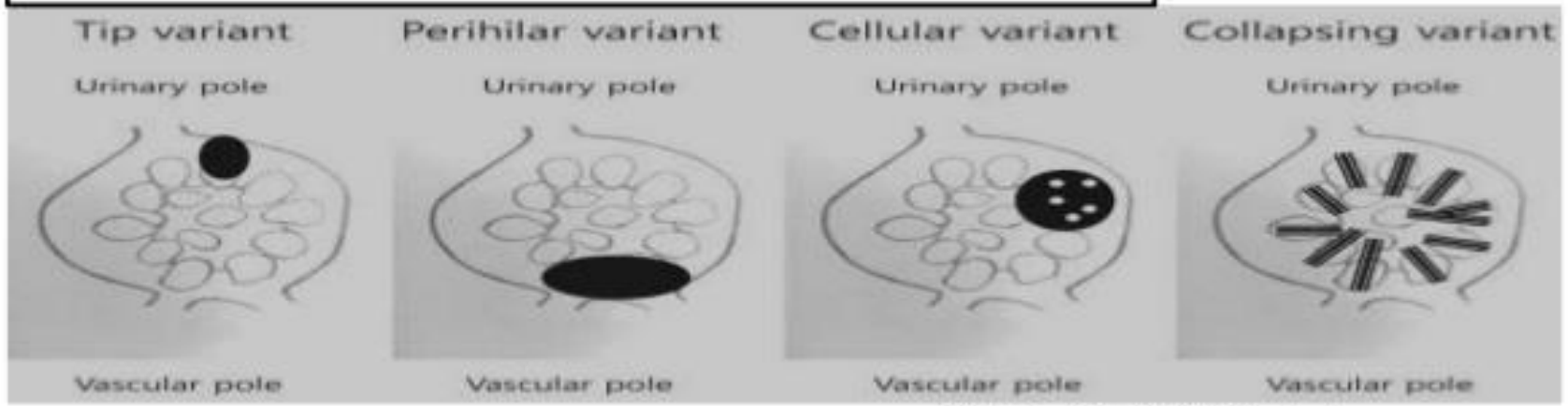
- **Classic or FSGS not otherwise specified (NOS)**: characterized by segmental areas of mesangial collapse and sclerosis in some but not all glomeruli
- **Collapsing**: can be induced by HIV infection and is distinguished by collapse and sclerosis of the at least one entire glomerular tuft *(clinically worst outcome)*
- **Tip**: segmental lesion that occur at the "tip" of the glomerulus near the origin of the proximal tubule *(behave like MCD-present acutely and respond to steroids)*
- **Cellula**r: presence of at least one glomerulus with segmental endocapillary hypercellularity that occludes the capillary lumen
- **Perihilar**: Sclerosis of >50% glomeruli at glomerular vascular pole *(common in secondary FSGS)*

Best prognosis for the "tip" variant and worse for "collapsing"

Pathological Variants

- **Tip variant**
  - Involving the part of the glomerulus near the origin of the proximal tubule
- **Perihilar variant**
  - Sclerosis of the vascular pole
- **Cellular variant**
  - Hypercellularity of the capillary space
- **Collapsing variant**
  - With ≥1 glomeruli with global or segmental collapse

Progress more rapidly to ESRD



Reidy K., et al. *Pediatr Nephrol.* 2007;22:350-54

TREATMENT OF FSGS

- *Important to differentiate primary from secondary FSGS: > 80% foot process effacement in primary (lesser in secondary FSGS) with no obvious cause for glomerular injury/ hyperfiltration /hypertension*
- Primary FSGS: Upto 40 to 60% achieve complete or partial remission with prednisolone (not secondary FSGS though)
- Concerns with big dose of steroids or steroid dependent or steroid resistant disease: Calcineurin inhibitor (Tacrolimus or Cyclosporine)
- FSGS relapse in transplant kidney: plasmapheresis and rituximab after ruling out secondary FSGS

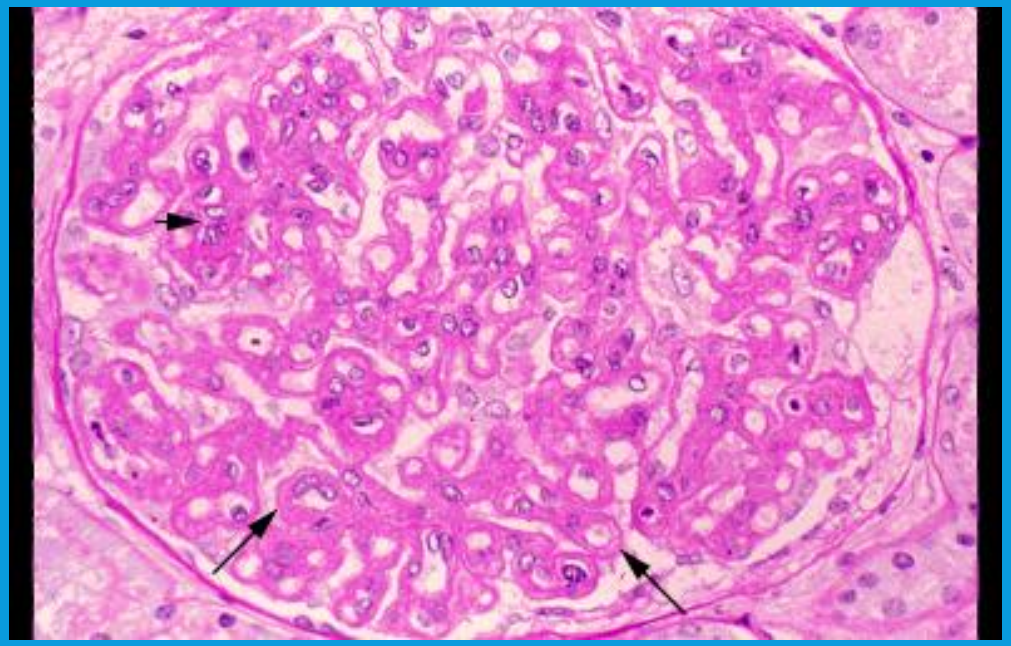
MEMBRANOPROLIFERATIVE (MPGN) OR MESANGIOCAPILLARY (MCGN)

- Characterised by increased **mesangial and endocapillary cellularity (proliferative lesions)** with **thickened GBM leading to a double-contour appearance**
- Immune complex-mediated MCGN: *chronic antigenemia causing activated classical complement pathway*
  - Infections: **HCV (often causing cryoglobulinemia), HBV**, Infective endocarditis, HIV, malaria, schistosomiasis
  - Autoimmune disorders: **SLE**, Sjogren's syndrome, Rheumatoid Arthritis
  - Monoclonal Gammopathies: **Myeloma, MGUS, MGRS**
- Complement mediated: *persistent activation of the alternative complement pathway*
  - Associated with C3Nef (with/without partial lipodystrophy/retinal defects)
  - Inherited mutation of Factor H
  - Monoclonal Gammopathies (commoner in adults)

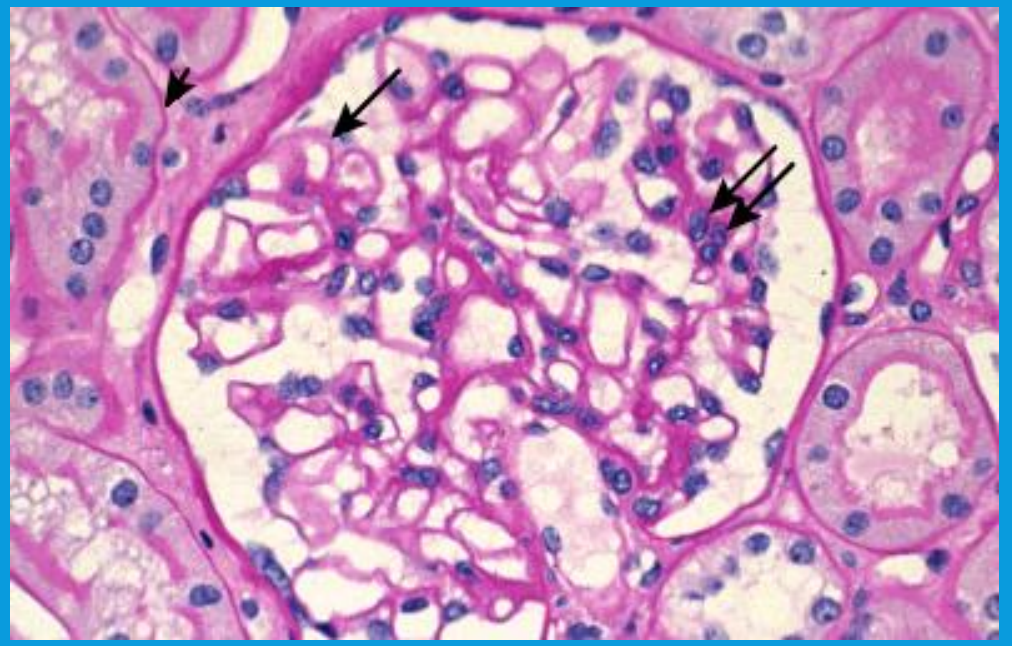
IMMUNE COMPLEX MEDIATED MCGN

- Associated with chronic antigenemia and/or circulating immune complexes **(chronic infections e.g.Hep C or B, autoimmune diseases and monoclonal gammopathies)**
- Glomerular deposition of immune complexes leads to activation of classical pathway **(normal or mildly low C_3 and low C_4 levels)**
- LM shows increased mesangial and endocapillary cellularity (leading to less open capillaries visible) and thickened GBM (often tram track)
- EM typically shows subendothelial and mesangial deposits (occ. subepithelial)
- **Co-existence of cryoglobulinemia common in Hep C and B associated MCGN**

IF MEDIATED MCGN



MCGN: LM showing thickening of all capillary walls with double contours (long *arrows)* and focal areas of cellular proliferation (short arrow)



LM of a normal glomerulus

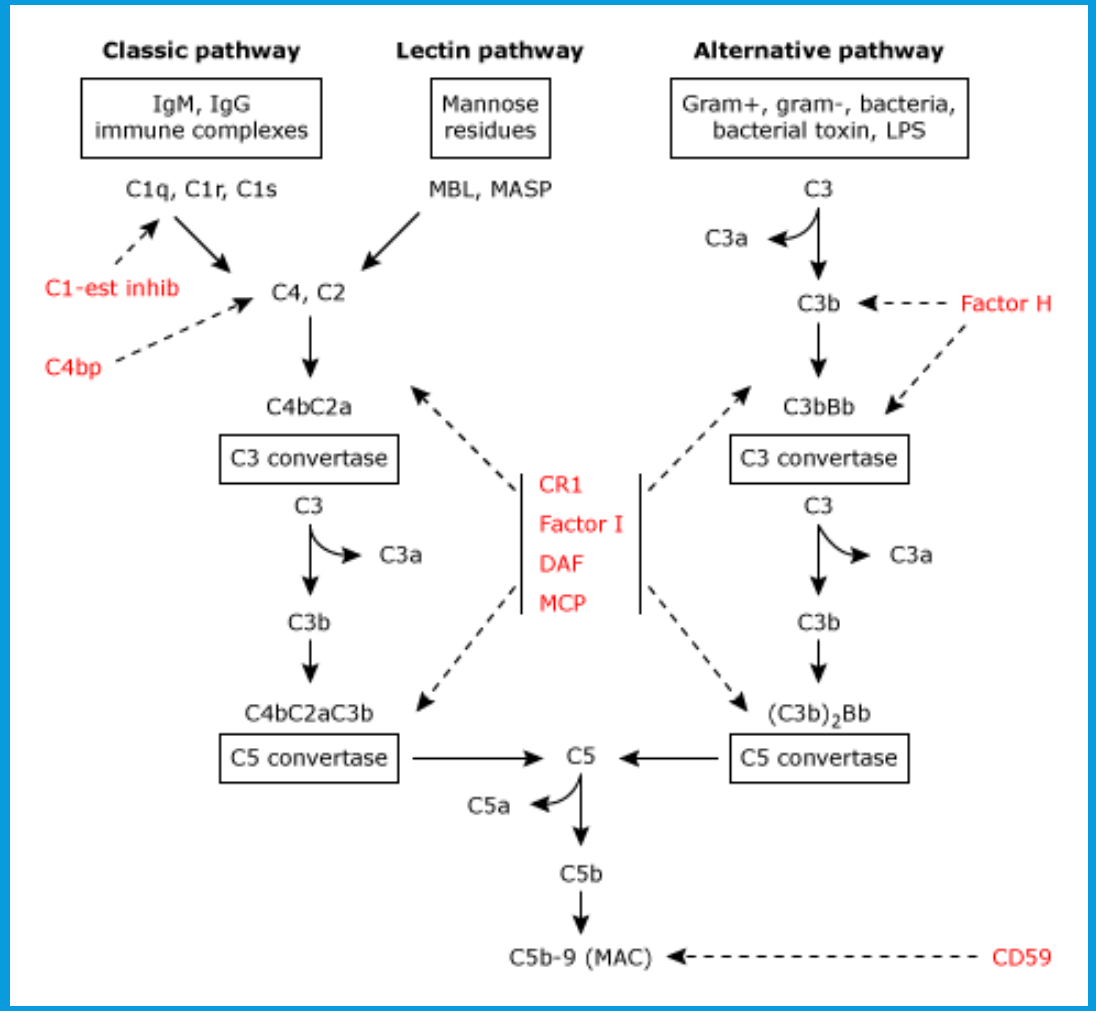
COMPLEMENT MEDIATED MCGN (INCLUDES DENSE DEPOSIT DISEASE AND C_3 GN)

- **Pathogenesis involves excessive activation of alternate complement pathway**

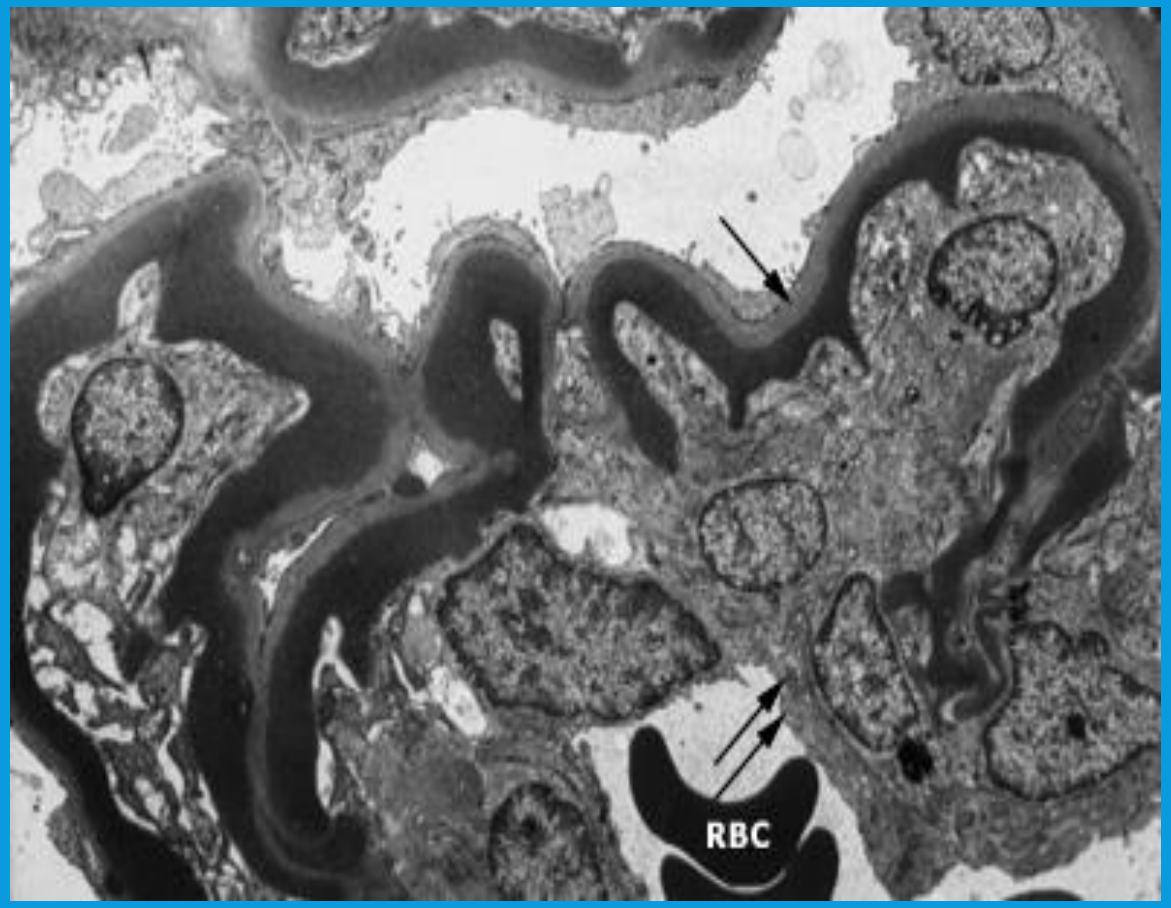
(so low serum C_3 but normal C_4)

- May involve antibodies to C_3 convertase (called C_3 nephritic factor) that stabilize the C_3 convertase by preventing its degradation by factor H or loss of function of the C_3 convertase inhibitory factor H (rarely deficiency of serum factors I or MCP)
- Commoner in children and young adults **(1 in 4 of young patients have complement factor gene variants)**
- EM (similar to IF mediated MCGN): subendothelial and mesangial electron-dense deposits(occ. subepithelial deposits)
- Dense deposit disease (DDD)reflects dense linear-appearing electron-dense material in the GBM (on EM)
- Some with DDD have partial lipodystrophy or visual defects (drusen bodies- mottled retinal pigmentation)

INHIBITORS OF ALTERNATIVE PATHWAY: FACTORS H AND CO-FACTOR FACTOR I



c mediated mcgn (dense deposit disease): em shows the dense, ribbon-like appearance of subendothelial and intramembranous material (arrow) and narrowing of the capillary lumen due to the proliferation of cells (double arrow).



MCGN – NEPHROTIC OR NEPHRITIC?

- Microscopic haematuria with non-nephrotic proteinuria (35%)
- Nephrotic syndrome with minimally depressed GFR(34%)
- Chronic progressive GN(20%)
- Rapidly progressive GN(10%)

TREATMENT OF IMMUNE COMPLEX MEDIATED MCGN

- Supportive therapy as in all NS i.e. antiproteinuric and antihypertensive
- Identification and treatment of aetiology e.g. anti-HCV therapy and **no immunosuppression**
- In case of severe cryoglobulinemia with HCV advised immunosuppression for 1 to 4 months with/without plasma exchange before starting anti-viral
- Idiopathic cases treated with immunosuppression including prednisolone and CNIs, cyclophosphamide or MMF

TREATMENT OF C MEDIATED MCGN

- *Give usual nephrotic syndrome therapy i.e., antiproteinuric and antihypertensive agents*
- No major RCTs done as relatively rare disease
  - Patients with proteinuria >1.5g/day and/or abnormal kidney function (but not rapidly progressive disease) offered mycophenolate and prednisolone **and** eculizumab (monoclonal IgG antibody that binds to complement protein C5) followed by plasmapheresis in non-responders
  - For Factor H deficiency- plasma infusion every 2-3 weekly
  - Patients with C3 glomerulopathy with monoclonal gammopathy offered chemotherapy
- Limited experience with transplant; relapse rates quite high especially in DDD

Am J Kidney Dis. 2019 Mar;73(3):316-323. doi: 10.1053/j.ajkd.2018.09.002. Epub 2018 Nov 7. Kidney Transplantation in C3 Glomerulopathy: A Case Series. Regunathan-Shenk R, Avasare RS, Ahn W, Canetta PA, Cohen DJ, Appel GB, Bomback AS

THANK YOU

"There are only two ways to live your life.

One is as though nothing is a miracle.

The other is as though everything is a miracle."

Albert Einstein