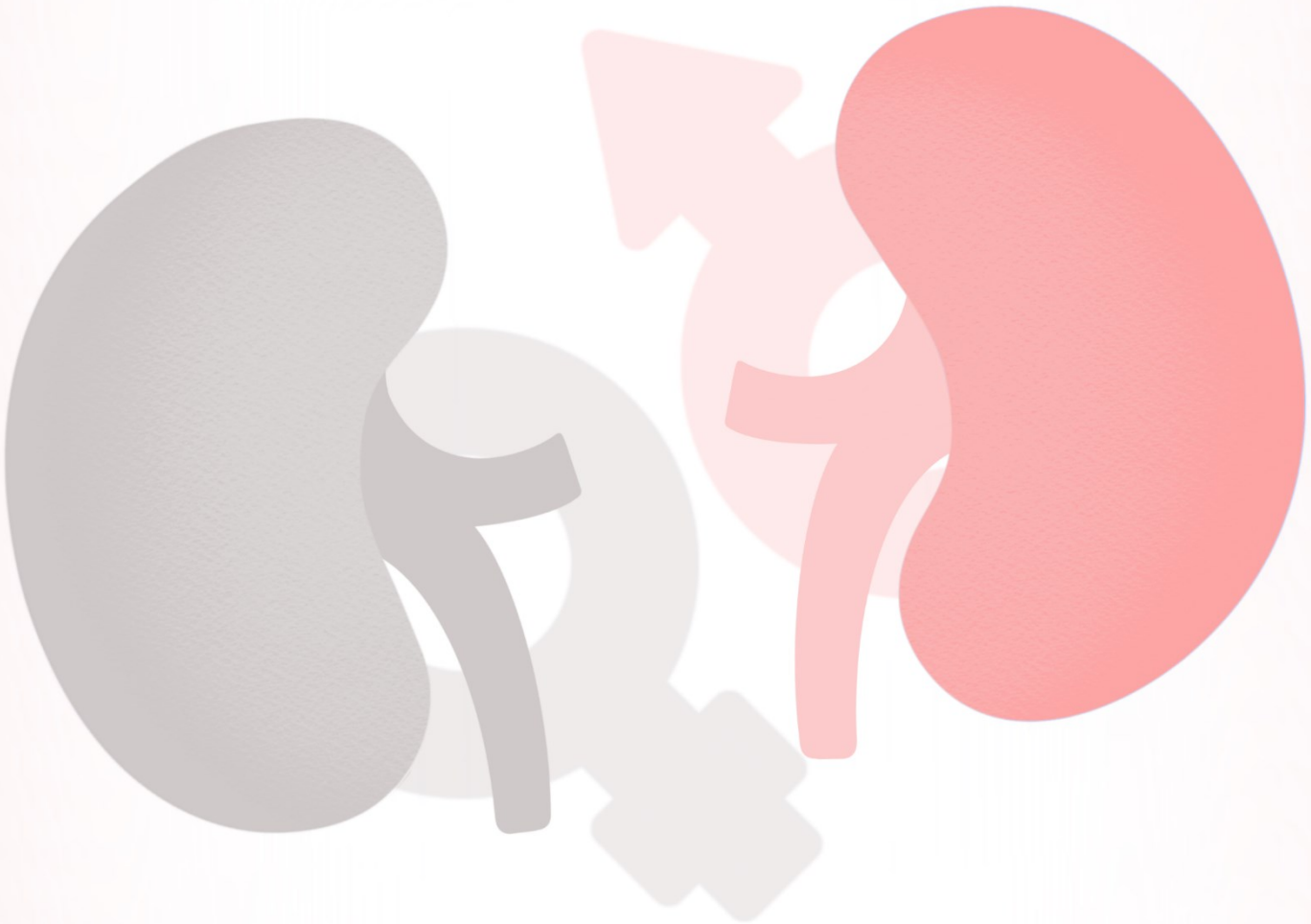
G.U.S.

3

Pathology



Sheet: Nephrotic Syndrome

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Nephrotic Syndrome

- Nephrotic Syndrome is a collection of symptoms and manifestations resulting from glomerular diseases. It includes the following features:

1. Massive proteinuria: large amounts of protein lost in urine (3.5 gm/day in adults).
   Normally, the filtration membrane prevents proteins (large proteins) from being filtered through the kidneys, thus they shouldn't be found in urine.
   However, in nephrotic syndrome, there is damage to the filtration membrane allowing the escape of proteins into urine, resulting in massive proteinuria.
   Massive proteinuria is the hallmark of Nephrotic Syndrome and is the cause of almost all other manifestations of the disease.

2. Hypoalbuminemia (≤ 3 gm/dL): One of the proteins lost is albumin, which results in low levels of albumin in the blood.

3. Generalized edema: It develops as a result of decreased colloid osmotic pressure (oncotic pressure). Albumin molecules are responsible for the majority of this oncotic pressure. Therefore, hypoalbuminemia would dramatically decrease the oncotic pressure.

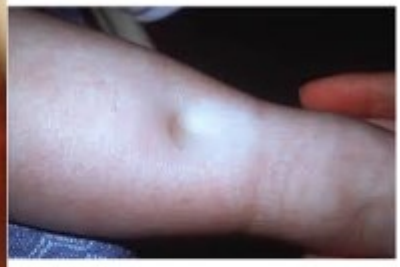
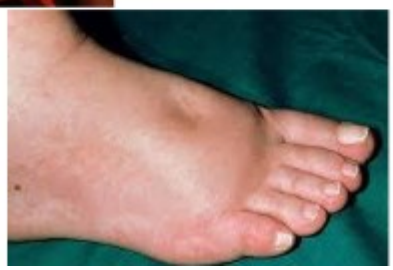
4. Hyperlipidemia, increased levels of lipids in the blood (LDL & Triglycerides), and lipiduria (which is abnormal).
   Why? One of the theories suggests that the increased synthesis of lipoproteins in the liver is due to shift in the metabolic pathways favoring synthesis of lipoproteins instead of albumin.
   Another theory suggests that albumin is the cause, because one of the functions of albumin is transport of lipids the blood. So, if there is hypoalbuminemia, lipids would accumulate in the blood.

5. Little or no azotemia (high BUN and creatinine indicating impaired renal functions), hematuria, and hypertension. This is in contrast to another similar disease called Nephritic syndrome which we will talk about in the next lecture.

Presentation

- Patients usually seek the physicians because of the generalized edema (in the abdomen and both upper and lower limbs), puffiness of the face, eyes, and lips.
- The physician would start investigating potential causes of the edema and begins by taking a blood pressure reading because of the possible cardiovascular causes of edema and some other renal disorders.
  CLUE 1: No hypertension is noted.

❖ Then, the physician orders a lab test for kidney function tests (KFTs) and urine analysis.
Kidney function tests (KFTs) are tests that assess the functional level of the kidneys. The two most important ones are creatinine and urea levels in blood.

CLUE 2: Urine analysis yielded positive results for massive proteinuria (3.5 mg).

CLUE 3: KFTs showed normal creatinine and urea levels.

The physician should start leaning toward a diagnosis of Nephrotic Syndrome due to the aforementioned CLUES.

Pathogenesis

❖ Several different diseases could result in nephrotic syndrome. But generally, it involves damage to the filtration membrane, either due to podocyte (podocytes have finger-like projections that cover the capillary wall from outside which is important for the impermeability of proteins) injury or injury to the glomerular basement membrane GBM.

Causes of Nephrotic Syndrome- two categories:

A. Primary glomerular diseases, such as:
1. Minimal-change disease
2. Focal segmental glomerulosclerosis (FSGS)
3. Membranous nephropathy
4. Membranoproliferative glomerulonephritis type 1 (usually a combination of nephrotic/ nephritic syndrome)

There is varying prevalence of these diseases in different age groups.

For example, minimal-change disease is the underlying cause in 65% of children diagnosed with nephrotic syndrome.

Meanwhile in adults, focal segmental glomerulosclerosis has the highest prevalence (35%).

Cause	Prevalence (%) Children	Prevalence (%) Adults
Primary Glomerular Disease		
Membranous GN	5	30
Minimal-change disease	65	10
Focal segmental glomerulosclerosis	10	35
Membranoproliferative GN	10	10
IgA nephropathy	10	15

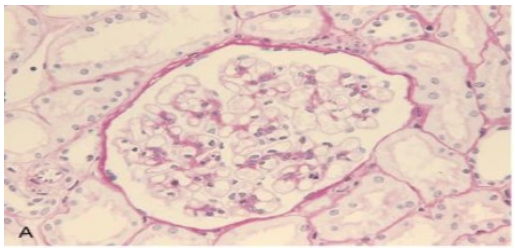
B. Secondary to systemic diseases with renal manifestations, such as:
   1. Diabetes mellitus
   2. Amyloidosis
   3. Systemic lupus erythematosus
   4. Drugs (gold, penicillamine, "street heroin")
   5. Infections (malaria, syphilis, hepatitis B, HIV)
   6. Malignancy (carcinoma, melanoma)
   7. Miscellaneous (e.g. bee-sting allergy)

*In this lecture we will focus on primary diseases.

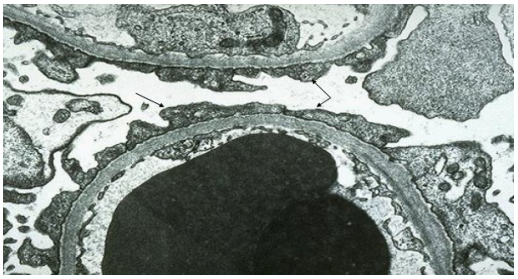
1- Minimal-Change Disease (Lipoid Nephrosis)

- It is called minimal change disease because there are minimal changes in the appearance of the glomeruli (in light microscope).
- Benign disorder (good prognosis).
- The most frequent cause of nephrotic syndrome in children (ages 1-7 years).
- Pathogenesis is still not clear. However, one of the theories suggests that T-cell derived factor causes podocyte damage and effacement (blunting) of foot processes. Thus, there will be loss of the function of the filtration membrane.

Morphology



- Light microscope: the glomeruli appear normal with a delicate basement membrane.
- Immunofluorescence: negative.
- Electron microscope: uniform and diffuse effacement of the foot processes of the podocytes & no immune deposits.

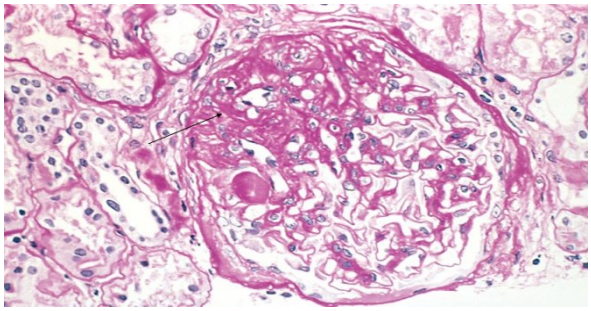


MCD - Clinical Course

- Nephrotic syndrome in an otherwise healthy child.
- No hypertension.
- Renal function preserved.
- Selective proteinuria (albumin).
- Prognosis is good in > 95% due to the ability of podocyte foot processes to recover.
- Less than 5% develop chronic renal failure after 25 years.
- Treatment: corticosteroids (90% of cases respond).
- In adults with minimal change disease, the response is slower and relapses are more common.

2- Focal and Segmental Glomerulosclerosis (FSGS)

- Name breakdown: sclerosis (fibrosis) affecting some, but not all, glomeruli (focal involvement) and involving only segments (not the whole) of the glomerulus (segmental).
- This image shows a mass of scarred, obliterated capillary lumens (CT/fibrous) with accumulations of matrix material.



- Usually causes nephrotic syndrome.
- It can occur:
    a. As a primary disease (20% to 30% of NS).
    b. Or secondary to AIDS, heroin abuse, nephron loss, inherited or congenital forms resulting from mutations affecting nephrin protein. etc....

Pathogenesis

- Still unclear, but could be due to injury to the podocytes, or sudden and severe elevations↑ in glomerular filtration rate (GFR), or due to genetic mutations affecting nephrin protein.

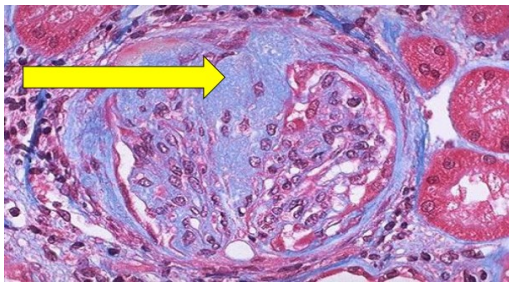
- There is damage to the filtration membrane leading to loss of proteins and, thus, nephrotic syndrome. With time, there is entrapment of plasma proteins and lipids in foci of injury where sclerosis develops.

Clinical Course

- Unlike the previous disease, FSGS has poor prognosis and about 50% of individuals end up with renal failure after 10 years.
- Poor responses to corticosteroid therapy.
- Adults do worse than children.

Morphology

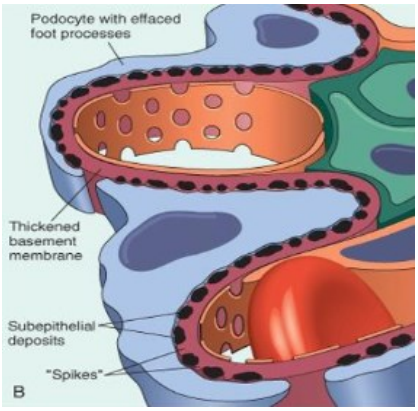
- LM: Sclerosis in some glomeruli (not all of them) and in a segment (not all of the affected glomerulus). Areas of collagen deposition appear blue in Masson's trichrome stain.
- IF: Negative.
- EM: Effacement of foot processes.



Collapsing glomerulopathy

- A morphologic type of FSGS.
- Poor prognosis.
- Collapse of glomerular tuft and podocyte hyperplasia.
- It may be: 1-idiopathic. 2-associated with HIV infection (IMPORTANT). 3- drug-induced toxicities.

3- Membranous nephropathy

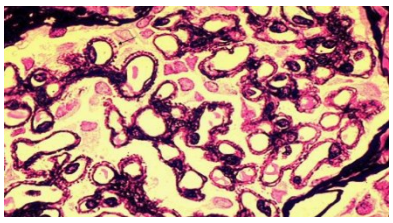


- It is an autoimmune disease where immune complexes (antigen & antibody together) deposit in the glomerulus, which disturbs the structure & function of the filtration membrane (loss of proteins), hence nephrotic syndrome.
- There is subepithelial (below the podocytes but above the GBM) deposits and the presence of "spikes" of basement membrane material between the immune deposits.
  The black spots on this image are the deposited immune complexes.

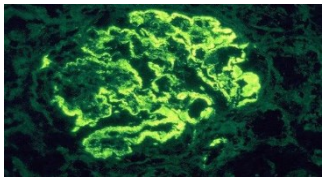
Types of Membranous glomerulonephritis:

1- Idiopathic (85% of cases): antibodies against podocyte antigen phospholipase A2 receptor (PLA2R) antigen.
2- Secondary.

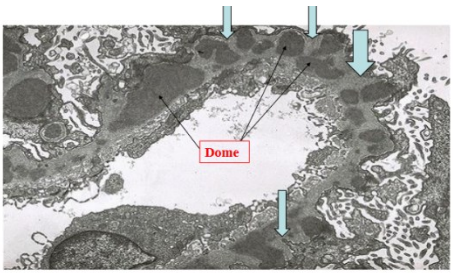
Morphology



- LM: diffuse thickening of the GBM, because of the deposited immune complexes. It appears black when using silver stain. Characteristic "spikes" are seen with membranous glomerulonephritis as projections around the capillary loops.



- IF: positive, deposits of immunoglobulins and complement along the GBM (IgG).



- EM: subepithelial deposits seen as "spike and dome" pattern.

Clinical Course

- Nephrotic syndrome.
- Poor response to corticosteroid therapy.
- Proteinuria persists in 60% of cases.
- Progressive disease and renal failure in 2 to 20 years in around 40% of cases.
- Partial / complete remission of proteinuria in 30% of cases.

MCD VS FSGS:

Not mentioned by the doctor.

	MCD	FSGS
hematuria	-	+
hypertension	-	+
proteinuria	selective	nonselective
response to corticosteroid therapy	good	poor

GOOD LUCK