RENAL PATH II

Renal Pathology, lecture II

Outline:

• Nephrotic syndrome – immune complex mediated
• Nephrotic syndrome non-immune complex mediated
• Nephrotic syndrome + hematuria

Nephrotic syndrome refers to a clinical complex that includes:
- massive proteinuria, with daily protein loss in the urine of 3.5 g or more in adults
- hypoalbuminemia, with plasma albumin levels less than 3g/dL
- generalized edema = most obvious clinical manifestation
- hyperlipidemia and lipiduria

Loss of protein with urine leads to hypoalbuminemia and a drop in plasma colloid osmotic pressure with edema.
It is presumed that hypoalbuminemia triggers increased synthesis of lipoproteins in the liver. Lipiduria reflects the increased permeability of the GBM to lipoproteins.

Nephrotic syndrome has diverse causes that share a common pathophysiology, leading to a derangement in the glomerular capillary wall, which results in increased permeability to plasma proteins.

The relative frequencies of different causes of nephrotic syndrome vary according to age. Also, nephrotic syndrome can be associated with primary glomerular diseases or can be a part of a systemic disease.
The primary diseases associated with nephrotic syndrome include membranous nephropathy, minimal change disease, focal and segmental glomerulosclerosis. Membranoproliferative and dense deposits disease usually are associated with nephrotic syndrome and hematuria. Systemic diseases with nephrotic syndrome, secondary to different mechanisms, include diabetes mellitus, amyloidosis and other (lecture III).

Membranous nephropathy:

1. Typical clinical presentation: edema, nephrotic syndrome, elderly can masquerade as cardiac failure; thrombosis (due to loss of anti-thrombin III), infections. In secondary membranous nephropathy there may be also s/s of an underlying disease
2. Epidemiology: young/middle age adults between 30 and 60 years of age. 30% adults, second most common nephrotic syndrome (children ~ 5%). 85% autoimmune, 15% secondary
   Auto-immune response against renal antigen (intrinsic or planted). It can be associated with carcinomas (lung, colon, breast, kidney, leukemia, non-Hodgkin’s
lymphoma, infections (malaria, hepatitis B and C, congenital syphilis, leprosy) or drugs (penicillamine, gold)

4. Pathology: no inflammation, no proliferation, capillary wall thickening with IgG + Complement granular subepithelial electron dense deposits and loss of foot processes

5. Laboratory tests: nephrotic syndrome (hypoalbuminemia, hyperlipidemia and lipiduria) with secondary hyperlipidemia, increased total cholesterol and low density lipoproteins (LDL) cholesterol, accelerated atherogenesis. There is no - NO complement drop since the process is chronic and relatively slowly progressing (“indolent”) such that the liver continues to replenish its loss.

6. Prognosis: variable with ⅓ of patients having spontaneous remission, ⅓ progressing to require dialysis and ⅓ third having proteinuria, without progression of renal failure

7. Treatment is difficult and may include immunosuppressive drugs (Prednisone) as well as non-specific anti-proteinuric drugs; in secondary membranous nephritis treatment of the underlying disease is carried out. Membranous nephropathy may recur after transplantation

Review introduction:
In membranous nephropathy subepithelial electron dense deposits lead to injury to visceral epithelial cells with effacement of foot processes and PROTEINURIA. There is no inflammatory reaction. Hence the preferred term is “nephropathy” rather than “glomerulonephritis”. Membranous nephropathy is a chronic immune complex mediated autoimmune disease linked to susceptibility genes and caused by antibodies to renal auto-antigen, or planted antigen.

Recent data regarding membranous nephropathy: several families were reported in which a neonate was found to be nephrotic and renal biopsies confirmed membranous nephropathy lesions. Subsequent evaluation showed mutations in neutral endopeptidase (NEP, an antigen normally found in the podocyte of the human glomerulus) of the mother. With pregnancy, the mother had formed antibodies to NEP, generated from the maternal circulation to the NEP antigen of the fetus. These anti-NEP antibodies crossed the placental barrier to the fetus and led to the in situ formation of immune complexes in the subepithelial space of the glomeruli in the kidney of the fetus; this resulted in damage to the GBM and the clinical findings of nephrotic syndrome in the newborn. These observations validated the in situ paradigm in human membranous nephropathy. Proteomic analysis of the target antigen in human “idiopathic”membranous nephropathy showed it to be the phospholipase A2 receptor (PLA2R) and thrombospondin type-I domain containing 7A (THSD7A). Most of the reactivity to PLA2R resides in the IgG4 subclass.

Membranous nephropathy – typical presentation:
• a young male develops edema: puffy eyes, shortness of breath, “shoes have been tight”
• there may be deep vein thrombosis (after a long plane trip) and a pulmonary embolus
• the patients may note urine becoming “foamy”
• UA: proteinuria 12 GM/24hrs, no hematuria
• Cholesterol 320 MG/DL
• Serum creatinine: 1.5 MG/DL [n=0.7-1.5]

Clinical diagnosis: nephrotic syndrome

Nephrotic syndrome non-immune complex mediated

Minimal change disease:

1. Typical clinical presentation: - edema (periorbital, generalized)
2. Epidemiology: children 2-6 yo, 65% of nephrotic syndrome in children; adults - 10% of nephrotic syndrome
3. Etiology/pathogenesis: reversible podocyte injury
4. Pathology: normal in paraffin sections, no immune complex deposits, foot processes effacement by electron microscopy
5. Laboratory tests: nephrotic syndrome
6. Prognosis: several episodes of nephrotic syndrome (relapses), normal renal function (!) and resolution @ puberty
7. Treatment: steroid sensitive

Minimal change disease typical presentation:
A 3 yo boy presented with periorbital and generalized edema. UA: proteinuria, 2.5 gm/24 hr. Clinical Dx: Nephrotic syndrome (NS)

Focal and segmental glomerular sclerosis (FSGS)

1. Typical clinical presentation: nephrotic syndrome with higher incidence of hematuria, reduced GFR, HTN and more often non-selective proteinuria
2. Epidemiology: adults 35% of cases of nephrotic syndrome, children 10%; higher incidence in African Americans and Hispanic patients
3. Etiology/pathogenesis: irreversible injury to podocytes
4. Pathology: segmental obliteration (sclerosis) of capillaries with collapse of capillary loops and increase in mesangial matrix. While initially only rare glomeruli are involved by sclerosis, with disease progression more glomeruli are involved and there is also progression to global sclerosis with tubulointerstitial scarring.
5. Laboratory tests: nephrotic syndrome, genetic testing in some patients
6. Prognosis: progression to renal failure
7. Treatment: initially nephrotic syndrome may respond to steroids (thus mimicking minimal change disease) but with disease progression there is steroids dependence and resistance. FSGS tends to recur in transplants.

Pathology of podocyte injury:
- reversible, manifested by effacement of the epithelial cell foot processes (minimal change disease)
- irreversible, associated with podocyte detachment, death and progressive obliteration of the affected capillary termed “sclerosis” (focal and segmental glomerular sclerosis)
- podocyte injury (podocytopathy) is also associated with alteration of the glomerular basement membrane charge with loss of its negative charge and, consequently, its permeability to negatively charged proteins such as albumin with severe proteinuria.

Heavy proteinuria, which is the hallmark of NEPHROTIC syndrome, can also be caused by subepithelial immune complex deposition.

It is not clear whether minimal change disease and FSGS represent one disease (but at opposite ends of a spectrum) or two different diseases.

FSGS typical presentation:
- A 10 yo boy at age 5 presented with NS, initially responding to steroids, subsequent relapses and decreased response to steroids, steroid-dependent, steroid-resistant
- Raising serum creatinine

The clinical diagnosis: nephrotic syndrome, clinically recurrent with renal failure

Terminology:
- focal (only some glomeruli involved) versus diffuse (all or nearly all/majority glomeruli involved)
- global (entire glomerular tuft involved) versus segmental (only some)

FSGS represents a common phenotype with diverse etiologies including cases which include the following:
3 most common forms: primary FSGS, adaptive FSGS, APOL1 FSGS
3 less common forms: genetic FSGS (high-penetration), medication-associated FSGS, and viral FSGS

- idiopathic FSGS is considered to be associated with a circulating cytokine, a putative “permeability factor”
- adaptive FSGS develops as an adaptive response to nephron loss/imbalance such that occurs in obesity, post renal ablation, reflux nephropathy, hypertension, body-building, low birth weight/premature birth, sickle cell disease, scarring of previously active lesions
- APOL1 FSGS associated with “risk alleles” in apolipoprotein L1 (APOL1) in African Americans; 70% of idiopathic FSGS cases in AA relate to APOL1 (see also below)
- virus-associated FSGS: HIV-associated, parvovirus B19
- medication/toxin associated FSGS: IFN, bisphosphonates, anthracycline, heroin
- genetic FSGS (high-penetrance) = mutations in genes encoding slit diaphragm proteins (nephrin, podocin) and other proteins

HIV-associated FSGS has a variant phenotype of FSGS which is termed “collapsing FSGS”. Collapsing FSGS has a very poor prognosis with rapid progression to renal failure, it accounts for 5-10% of FSGS

**APOL1 FSGS**

Development of high throughput technologies has opened up the opportunities for studying polygenic diseases. GWAS [genome-wide association studies] have been instrumental in the identification of the genetic component in polygenic diseases.

GWAS searches the *entire* genome for small variations, single nucleotide polymorphisms or SNPs (“snips”) that occur more frequently in people with a particular disease than in people without the disease. Thus, each study can look at hundreds or thousands of SNPs at the same time to pinpoint genes that may contribute to a person’s risk of developing a certain disease, “risk alleles”. Several common diseases in which many genetic variations contribute to a person’s risk, and which were identified by GWAS, include diabetes, heart abnormalities, Parkinson’s disease, Crohn’s disease, hypertension… It is hoped that, in the future, more SNPs associated with chronic diseases, and variations that affect a person’s response to certain drugs or influence interactions between a person’s genes and the environment, etc can be identified and thereby facilitate a truly “personalized medicine”.

To this end, recent studies have shown that genetic variants in the APOL1 gene account for a large fraction of the high rates of nondiabetic kidney disease in African Americans

APOL1 risk variants have large effects on several different types of kidney disease previously thought to be distinct entities: FSGS [Focal and Segmental Glomerular Sclerosis], HIV-associated nephropathy, severe lupus nephritis, sickle cell nephropathy and unspecified chronic kidney disease, often previously labelled as “hypertensive nephropathy in African Americans”

These variants, found only in individuals with recent African ancestry, (<10,000 years) confer enhanced innate immunity against African trypanosomes. These alleles are nearly absent in populations of European and Asian ancestry

APOL1 risk variants arose approximately 4,000 years ago in Africa and rose quickly to high frequency. In Nigeria, approximately 46% of chromosomes contain either the G1 or G2 allele. The ancestors of modern Europeans left Africa many millennia before the
origin of these risk alleles, so the risk alleles are not found in Europeans. Today, approximately 36% of all African Americans carry the G1 or G2 alleles. People who have at least 1 copy of either the G1 or G2 variant are resistant to infection by trypanosomes (protozoa), but people who have 2 copies of either variant are at an increased risk of developing a non-diabetic kidney disease. Genotype may be G1/G1, G2/G2, or the compound heterozygous state of G1/G2

*The presence of the alleles is not enough to have the phenotype. These are risk alleles rather than single-gene disorders and additional “hits” are necessary, which may be genetic, environmental, or both. This, however, provides an opportunity for the development of preventive measures for those at risk.*

Lessons learned from these studies indicate that:
- genetic differences substantially influence an individual’s lifetime risk for kidney disease
- evolution of genes related to host defense against pathogens may limit kidney longevity
- expanding our understanding of renal development and function may enable the design of novel therapeutics for kidney disease as well as preventive measures for those at risk

*The variants have proven to be useful for genetic screening in African Americans and in the selection of kidney donors*

FSGS summary:
FSGS is the most frequent morphologic manifestation of glomerular injury seen in human biopsy material and it’s incidence continues to increase and leads to renal failure. FSGS is a consequence of a shared pathogenic pathway where different etiologies lead to similar types of injury.

In children FSGS = 10%, in adults = 35% of nephrotic syndrome patients with primary glomerular diseases.

Nephron loss
Once renal disease, glomerular or otherwise, destroys sufficient nephrons to reduce the glomerular filtration rate to 30-50% of normal, progression to end stage renal disease proceeds at varying rates via scarring, called glomerulosclerosis
Adaptive changes in response to the loss of nephrons at this stage are ultimately maladaptive and exacerbate progressive sclerosis

**Nephrotic syndrome + hematuria**

Membranoproliferative glomerulonephritis (MPGN) and Dense Deposit Disease (DDD)
Previously termed MPGN type I and II respectively, now recognized as distinct diseases.
Membranoproliferative glomerulonephritis (MPGN):

1. Typical clinical presentation: nephrotic syndrome + hematuria
2. Epidemiology: older children (10%), adults (10%)
3. Etiology/pathogenesis: primary immune complex formation with classical complement activation in response to unknown antigen? Secondary to chronic autoimmune disorders such as hepatitis, endocarditic or chronic bacterial infections or associated with underlying B cell/plasma cells clonal proliferation with production of monoclonal protein (aka paraprotein).
4. Pathology: lobular tufts, thick glomerular basement membrane and IgG+complement subendothelial deposits
5. Laboratory tests show low complement
6. Prognosis is poor with progression to renal failure
7. Treatment: difficult, treatment of an underlying disease when feasible

Dense Deposit Disease (DDD) (formerly MPGN type II)

1. Typical presentation with nephrotic syndrome and hematuria
2. Epidemiology: rare, affecting older children
3. Etiology/pathogenesis: there is a sustained activation of complement via alternative (i.e. non-antibody mediated) pathway; there is no antibody formation per se.
4. Pathology: only complement is detectable by immunofluorescence (without accompanying immunoglobulin) and electron microscopy is diagnostic in demonstrating dense deposits within the lamina densa of the glomerular capillary wall.
5. Laboratory tests: complement is low; molecular studies are becoming available in specialized laboratories
6. Prognosis is poor with progression to renal failure; there is also a high rate of recurrence in transplants
7. Therapies: new therapies being developed involve control of complement activation

Glomerular diseases caused by complement activation in the absence of antibody: there is unregulated/excessive activation of the alternative complement pathway leading to complement-mediated injury (transformation from low-grade physiologic activity [“tick-over”] to unrestrained hyperactivity).

Triggers: excessive complement activation after minor vascular injuries
- acquired autoantibodies against complement components
- inherited abnormalities of complement regulatory proteins

Human diseases
Glomerular: dense deposit disease/C3 glomerulonephritis
Systemic (with significant renal manifestations): thrombotic microangiopathies (lecture III)

Lecture I and II summary:
Glomerular diseases associated with

1. nephritic syndrome/hematuria: postinfectious, IgA nephropathy, hereditary
2. severe nephritic syndrome and rapidly progressive renal failure types I, II, III
3. nephrotic syndrome immune complex mediated: membranous nephropathy
4. nephrotic syndrome of unknown, non-immune complex-associated pathogenesis: minimal change disease and FSGS
5. nephritic syndrome and hematuria associated with primary immune complex formation with classical complement activation: membranoproliferative glomerulonephritis
6. nephritic syndrome and hematuria associated with unregulated/excessive activation of the alternative complement: dense deposit disease