“The evolution of the classification of nephrotic syndrome and the new taxonomy for the podocytopathies”

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Old classification schemes:

Proteinuria and nephrotic syndrome

- MCD
  - Good prognosis and Response to steroid Therapy
  - Poor prognosis and Poor Response to Steroid therapy
- FSGS
Nephrotic syndrome - the 80’s and 90’s

- While the definition of minimal change disease did not change over the years, in the mid 80’s other patterns of glomerular damage have became part of the FSGS spectrum.

- **Collapsing glomerulopathy:**
  - first description in 1978 as “malignant FSGS” (Brown Clin Nephrol 1978)
  - 1980’s frequent diagnosis during HIV pandemic (HIV-AN)
  - in mid 90’s became “idiopathic collapsing FSGS” (Detwiler et al KI 1994 & Valeri et al JASN 1996)

- **Cellular lesion:**
  - Term used first by Schwarz and colleagues to indicate a group of lesions with endocapillary and/or extracapillary increased cellularity.
  - Other authors used the term cellular to indicate intracapillary cellularity only.

- **Tip lesion:**
  - Howie et al described tip lesion as a well-defined and specific pathological entity with clinical similarity to MCD. (J Pathol 1984)
  - Tip lesions are also seen in associations with other glomerular diseases such as diabetic nephropathy or membranous glomerulopathy.
Relatively recent classification schemes: Columbia classification - FSGS variants

- Perihilar
- NOS
- Tip

- Cellular
- Collapsing
Limitations of the morphologic classification

• Various histopathologic lesions are listed under “focal segmental glomerulosclerosis” regardless the presence or absence of segmental sclerosis.

• Lack of correlation with pathogenetic mechanisms and etiology.

• Lack of correlation with treatment
Proteinuria and nephrotic syndrome in the 21\textsuperscript{st} century

- The attention of scientists, nephrologists and pathologists has been recently focused on the role of podocytes as cause of proteinuria

- In the last 10 years lot of progress has been made in the understanding the biology of podocytes, how they function and how they are injured.

“Taxonomy of the podocytopathies”
where morphologic diagnosis are integrated with etiology

(Barisoni, Schnaper, Kopp, CJASN 2007)
**Podocytopathies**

**DEFINITION:** Proteinuric diseases in which pathologic processes arise from intrinsic or extrinsic “primary” podocyte injury and where the podocyte genotype/phenotype is altered.
A taxonomy is organized into multiple levels, each of which represents a taxon with one or more elements (taxa), which are mutually exclusive, unambiguous, and all-encompassing categories.

Taxonomies provide classification and conceptual framework for analysis, discussion, and hypothesis generation.
Podocytopathies:
4 morphologic patterns of glomerular injury

- Normal Histology
- Segmental Sclerosis
- Mesangial Sclerosis
- Collapse of the GBM

MCN
FSGS
DMS
CG
Common denominator of podocytopathies: Podocyte injury = foot process effacement

(a) Normal: Foot processes are well-defined and distinct.
(b) Effacement: Foot processes are flattened and indistinct.

GBM (Glomerular Basement Membrane)
Causes of foot process effacement

1. Impaired formation of the slit diaphragm complex
2. Abnormalities of the adhesive interaction between podocytes and GBM
3. Alterations of transcription factors
4. Abnormalities of the actin-based cytoskeleton
5. Alterations of the apical domain of podocytes
6. Mitochondria abnormalities
7. Abnormalities of cell metabolism
8. Mechanical stress
9. Viral infection
10. Acute ischemic injury
11. Toxic / metabolic effect
12. Immunologic stimuli
How do we translate this large variety of insults into four morphologic patterns of glomerular injury?
Hypothesis #1: Injured podocytes can take different pathways

Podocyte injury

- Altered phenotype
  - No change in podocyte number
    - No change
      - MCN

- Engagement of apoptotic pathways
  - Cell death
    - Segmental sclerosis
      - FSGS

- Developmental arrest
  - Proliferation (low)
    - Mesangial sclerosis
      - DMS

- De-differentiation
  - Proliferation (high)
    - Collapse
      - CG
The role of the renopoietic system

Hierarchical distribution of CD133+CD24+PDX- and CD133+CD24+PDX+ cells within human glomeruli

Hypothesis #2
The role of CD24+CD133+ renal progenitors in FSGS & CG.

Podocyte injury

- Altered phenotype
  - No change in podocyte number
    - MCN

- Podocyte death
  - CD24+CD133+ Repair activity
    - Segmental sclerosis
      - FSGS

- Developmental arrest
  - Proliferation (low)
    - Mesangial sclerosis
      - DMS

- Podocyte death
  - Exuberant CD24+CD133+ Activity
    - pseudocrescents

- No change in podocyte number
  - FSGS

- CG
MINIMAL CHANGE NEPHROPATHY
Minimal Change Nephropathy

DEFINITION
Normal histology.
Extensive foot process effacement, but preserved number of podocytes.

ETIOLOGY AND CLINICAL ASSOCIATION

• Idiopathic
• Inherited
  - Non-Syndromic (NPHS1, NPHS2)
  - Syndromic (DYSF)
• Reactive
  - drug-induced
    (NSAID, pamidronate, interferon, others)
  - dysregulation of the immune system
  - hematologic malignancy
Minimal change nephropathy

- **Reversible – Steroid sensitive**
  - idiopathic
  - reactive (secondary)
    - drug-induced (NSAID, pamidronate, interferon, others)
    - dysregulation of the immune system
    - hematologic malignancy

- **Irreversible - Steroid resistant**
  - idiopathic
  - genetically determined
    - NPHS2
    - DYSF
Can pathologists discriminate between steroid sensitive and steroid-resistant MCN?
Glomerular expression of dystroglycans is reduced in MCD but not in FSGS

Regele JASN11:403-412, 2000

α-dystroglycan  β-dystroglycan  β₁-integrin

Normal kidney

FSGS

MCD
DG staining in steroid sensitive and steroid resistant MCN

Laura De Petris, David Thomas, Helen Liapis, Laura Barisoni

Fig 1

IHC staining

negative

positive

☐ FSGS  ◊ Ctrl  ▲ SR-MCN  ○ SS-MCN  △ MCN (no f-up)
Podocin: control

Podocin: steroid-resistant MCN
FOCAL SEGMENTAL GLOMERULOSCLEROSIS
FSGS

DEFINITION

Segmental solidification of the tuft accompanied by sinechiae. Hyalinosis and foam cells can also be present. Low number of podocytes (podocytopenia).

ETIOLOGY AND CLINICAL ASSOCIATION

- **Idiopathic**
- **Inherited**
  - syndromic
  - non-syndromic
- **Reactive**
  - hyperfiltration-mediated
    - normal renal mass
    - reduced renal mass
  - medication-induced
  - permeability factor (?)
Idiopathic FSGS

Is idiopathic really idiopathic?

**MYH9 is a major-effect risk gene for FSGS.**

*(Kopp et al. Nat Genet. 2008)*

MYH9 risk alleles are more frequent in AA. MYH9 protective alleles are more frequent in EA.
Genetic forms of FSGS

• Associated with other organ abnormalities (syndromic):
  – Freiser Syndrome (WT-1).
  – Nail-patella syndrome (LMX1B)
  – Renal-coloboma syndrome with oligomeganephronia (PAX2)
  – Alport’s disease (COL4A3, A4, A5)
  – Metabolic disorders (GLA – Fabry’s)
  – Mitochondriopathies (mtDNA tRNA^{Leu} and tRNA^{Tyr}, CoQ2 NP, CoQ6 NP)

• Limited to the kidney (non-syndromic):
  - NPHS1 – nephrin – autosomal recessive
  - NPHS2 – podocin – autosomal recessive
  - NPHS3 – phospholipase Cε1 – autosomal recessive
  - CD2AP – susceptibility to FSGS
  - MYH9 – susceptibility to FSGS
  - ACTN4 – α-actinin-4 - autosomal dominant
  - INF2 – autosomal dominant
  - TRPC6 – Transient Receptor Potential channel 6 - autosomal dominant
  - WT1 – sporadic/isolated FSGS
Reactive forms: Hyperfiltration-mediated FSGS

glomerulomegaly in pt with single kidney

Segmental sclerosis

large non-sclerotic glomerulus
Which is the relationship between glomerulomegaly and FSGS?
FSGS: From podocyte hypertrophy to podocytopenia.


In response to increased glomerular volume, podocytes undergo hypertrophy though 5 stages.

- **Stage 1**, normal podocyte;

- **Stage 2**, non-stressed hypertrophy;

- **Stage 3**, "adaptive" hypertrophy: changes in synthesis of structural components but maintenance of normal function;

- **Stage 4**, "de-compensated" hypertrophy
  - reduced production of proteins necessary for normal podocyte function.
  - widened foot processes and decreased filter efficiency (proteinuria);

- **Stage 5**, podocyte numbers decrease.

Dr Kriz’s model
DIFFUSE MESANGIAL SCLEROSIS
DMS

DEFINITION:
Diffuse increase of mesangial matrix accompanied by mild proliferation of hypertrophic podocytes.

ETIOLOGY:
• Idiopathic
• Genetic
  - Non-syndromic
    - WT1
    - NPHS1
    - NPHS2
    - NPHS3
    - COQ6
  - Syndromic
    - LAMB2 (Pierson S.)
    - WT-1 (Denys-Drash S.)
WT-1 associated DMS

• Reduced or dysfunctional expression of WT-1, a podocyte transcription factor.
• Increased expression of growth-promoting molecules (Pax-2, Ki-67).
• Podocyte entry into the cell cycle.
• Preservation of other podocyte markers (nephrin, synaptopodin, α-actinin-4).
Chromosome 10q23.32-q24.1 = phospholipase Cε1.

**Truncating mutations**
- Developmental arrest
  - DMS: early onset of severe NS and rapid progression to renal failure.

**non-truncating missense mutations**
- Podocytopenia
  - FSGS: later onset of NS and slower progression to renal failure.

Of Note: 2 pts responded to steroid and Cyclosporin A.

*Hinkes et al. Nat Genetic 2006*
COLLAPSING GLOMERULOPATHY
CG Definition: GBM collapse and pseudocrescent formation
CG: etiology and clinical associations

- **Idiopathic**
- **Genetic**
  - Syndromic - action myoclonus renal failure
  - Non-Syndromic - CoQ2 NP
- **Reactive**
  - Virus associated
    - HIV
    - parvovirus B19
    - CMV
  - Infections - filariasis
    - leishmania
    - TB
  - Autoimmune - Still’s disease
    - lupus like
    - RA
    - mixed connective tissue
  - Malignancy (myeloma, AML)
  - Medications - pamidronate
    - interferon
    - valproic acid
  - Vascular insult - TMA
  - Permeability factor
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<th></th>
<th>idiopathic</th>
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<td></td>
<td>• Steroid-sensitive</td>
<td>• <em>NPHS1</em></td>
<td><em>(immunologic stimuli, Tumors)</em></td>
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<td>• Steroid-resistant</td>
<td>• <em>NPHS2</em></td>
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<td>• <em>DYSF</em></td>
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<td>• Steroid-sensitive</td>
<td><strong>ITGB4, NPSH2, NPHS3, NPHS1 + NPHS2, COQ2, MHY9, ACTN4, CD2AP, TRCP6, WT-1, SYNPO, INF2</strong></td>
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<td>• Steroid-resistant</td>
<td><strong>Syndromic</strong></td>
<td>• Initially normal nephron mass</td>
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Proteinuria and nephrotic syndrome – the present

- MCN, FSGS, DMS and CG are patterns of glomerular damage where the common denominator is podocyte injury.

- Morphologic classifications alone are insufficient to capture the complexity and heterogeneity of diseases presenting with NS.
  - multiple specific disease processes can present with indistinguishable histopathology
  - a specific monogenetic disorder can present with more than one form of histopathologic pattern of glomerular damage.

- Final diagnosis of the podocytopathies should occur in 3 steps:
  a. clinical evaluation
  b. morphologic evaluation
  c. additional clinical tests, such as genetic or serology for evidence of infections, or others, when indicated.

Proteinuria and nephrotic syndrome – the future

**NEPTUNE** – international effort with the following major goals:

- Determination of rates and predictors of clinical remission or progression in NS
- Identification of gene expression profiles
- Identification of patient specific molecular signatures
- Clinically useful classification based on morphologic & molecular phenotype