FSGS and Nephrotic Syndrome

Kirk Campbell, M.D.
Thanks to our speaker!

Kirk Campbell, M.D.

- Associate Professor of Medicine, Vice Chair for Diversity and Inclusion and Director of the Nephrology Fellowship Program at Icahn School of Medicine at Mount Sinai
- In addition to treating patients with renal disease, Dr. Campbell leads an NIH-funded research program focused on understanding the mechanism of podocyte injury in the progression of proteinuric kidney diseases.
- He actively participates in clinical trials testing novel agents for primary glomerular disease.
- Prior Nephcure Foundation Young Investigator Awardee
Objectives

• Explain proteinuria (protein in urine)
• Define nephrotic syndrome
• Describe the features and development of FSGS
• Discuss current and upcoming treatment options
Why is this topic important?
Kidneys remove waste and fluid in urine
Proteinuria = protein in the urine
Burden of proteinuric kidney disease

~ 90% of ESKD

~$20 billion/year expenditure

Wiggins, Kidney Int 2007
Proteinuric kidney disease as a cause of death in the US

Table B. Deaths and death rates for 2010, and age-adjusted death rates and percent changes from 2009 to 2010, for the 15 leading causes of death: United States, final 2009 and preliminary 2010

<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Accidents (unintentional injuries) (V01–X59, Y05–Y86)</td>
<td>118,043</td>
<td>38.2</td>
<td>74.1</td>
<td>41.6</td>
<td>-1.1</td>
</tr>
<tr>
<td>6</td>
<td>Alzheimer’s disease (F00–F03)</td>
<td>83,306</td>
<td>27.0</td>
<td>25.0</td>
<td>39.0</td>
<td>3.3</td>
</tr>
<tr>
<td>7</td>
<td>Diabetes mellitus (E10–E14)</td>
<td>68,905</td>
<td>22.3</td>
<td>20.8</td>
<td>21.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>8</td>
<td>Nephritis, nephrotic syndrome and nephrosis (N00–N07, N17–N19, N25–N37)</td>
<td>50,472</td>
<td>16.3</td>
<td>15.3</td>
<td>15.1</td>
<td>1.3</td>
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<tr>
<td>9</td>
<td>Influenza and pneumonia (U00–U04, J09–J18)</td>
<td>50,003</td>
<td>16.2</td>
<td>15.1</td>
<td>16.5</td>
<td>-8.5</td>
</tr>
<tr>
<td>10</td>
<td>Intentional self-harm (suicide) (X60–X84, Y87.0)</td>
<td>37,793</td>
<td>12.2</td>
<td>11.9</td>
<td>11.8</td>
<td>0.8</td>
</tr>
<tr>
<td>11</td>
<td>Septicemia (A41)</td>
<td>34,643</td>
<td>11.3</td>
<td>9.7</td>
<td>10.6</td>
<td>-3.6</td>
</tr>
<tr>
<td>12</td>
<td>Chronic liver disease and cirrhosis (K70, K73–K74)</td>
<td>31,802</td>
<td>10.3</td>
<td>9.4</td>
<td>13.3</td>
<td>-3.3</td>
</tr>
<tr>
<td>13</td>
<td>Essential hypertension and hypertensive renal disease (I10–I15)</td>
<td>29,117</td>
<td>8.6</td>
<td>7.9</td>
<td>8.6</td>
<td>1.3</td>
</tr>
<tr>
<td>14</td>
<td>Parkinson’s disease (G20–G21)</td>
<td>21,963</td>
<td>7.1</td>
<td>6.8</td>
<td>7.6</td>
<td>1.2</td>
</tr>
<tr>
<td>15</td>
<td>Pneumonia due to solids and liquids (J36)</td>
<td>17,001</td>
<td>5.5</td>
<td>5.1</td>
<td>6.9</td>
<td>4.4</td>
</tr>
</tbody>
</table>

... All other causes (residual) 488,954 158.5

CDC National Vital Statistics Report 2012
Regardless of CKD status, proteinuria increases chances of death

Anatomy of the glomerulus

Glomerulus: Tiny filter inside kidney
Podocytes = key target cells for injury
Nephrotic Syndrome

- Proteinuria greater than 3.5 grams/day
  - Too much protein leaving through the urine as a result of broken kidney filters
- Hypoalbuminemia (low albumin in blood)
- Hyperlipidemia (too much fat, such as cholesterol, in blood)
- Edema (swelling)
Nephrotic Processes

RENAL BIOPSY = PATTERN OF INJURY→
Light Microscopy, Immunofluorescence, EM

- Minimal Change Disease
- FSGS
- Membranous Nephropathy
- Other:
  - DM
  - Para-proteins (Amyloid)

Primary (idiopathic)
- HIV
- HTN, DM
- Obesity
- Low nephron mass
- Drugs

Secondary
- Infection (hep B, Hep C)
- Malignancy
- SLE/MCTD
- Drugs

Secondary
- HIV
- HTN, DM
- Obesity
- Low nephron mass
- Drugs

Genetic
What is FSGS?
Focal segmental glomerulosclerosis (FSGS) involves scars on some of your kidneys’ filters. The scarring makes it hard for your kidneys to filter out wastes from your body and can lead to kidney failure.

- FSGS: A histologic pattern of injury (not a “disease”)
  - Focal: Some (<50% or half) of glomeruli affected
  - Segmental: Only portion of affected glomerulus is sclerosed or hardened

1. Focal Vs Diffuse

2. Segmental Vs Global
FSGS

Normal Glomerulus
- Blood flows in
- Glomerulus (capillaries)
- Bowman’s capsule
- Urinary space
- Blood flows out
- Porous capillaries allow waste products to pass out into urinary space, creating urine
- Sufficient urine output

FSGS
- Scar tissue (sclerosis) around capillaries impedes removal of waste products
- Decreased urine output
FSGS
Causes of FSGS

**Mechanical stretch**
- Unilateral renal agenesis or hypoplasia
- Renal ablation—remnant kidney
- Obesity
- Reflux interstitial nephropathy
- Extensive nephron loss secondary to various renal diseases, including glomerulopathies
- Oligomeganephronia

**Viral infections**
- HIV-associated nephropathy
- Parvovirus B19
- Simian virus 40
- Hepatitis C virus
- Cytomegalovirus
- Epstein–Barr virus

**Hereditary conditions**
- Gene defects in the slit diaphragm (nephrin, podocin, CD2-associated protein, α-actinin 4)
- **WT1** mutation (Frasier syndrome)
- Mitochondrial cytopathies
- **SMARCA1** gene mutations (Schimke syndrome)

**Toxic agents**
- Heroin
- Pamidronate
- Lithium
- Interferon-α

**Ischemia (reduced blood flow)**
- Cholesterol crystal embolism
- Renal artery stenosis
- Malignant hypertension
- Hypertensive nephrosclerosis (especially in blacks)
- Calcineurin-inhibitor toxicity
- Renal-transplant rejection

**Aging**

**Congenital cyanotic heart disease**
Epidemiology
Kidney failure due to FSGS

Incidence data from USRDS

Kopp et al. Am J Kid Dis 2004
Increase in FSGS incidence

• New York: 1974-1993
  – Frequency of all forms of FSGS among renal biopsies increased 7-fold

• Chicago/Midwest: 1974-1993
  – Idiopathic (unknown cause) FSGS increased from 4% to 12% in adult biopsies
USRDS Stat

• FSGS is currently the most common primary glomerular disease causing kidney failure in the United States
What factors impact prognosis/outcome?
Prognosis/outcomes of Proteinuria

Korbet, Neph Dial Transpl 1999
Prognosis/outcomes – Renal function

Korbet, Neph Dial Transpl 1999
Genetics of FSGS
Familial or Genetic FSGS

- NPHS1 (nephrin) - AR
  Kestila et al., Mol Cell 1998
- NPHS2 (podocin) - AR
  Boute et al, Nat Genetics 2000
- PLCE - AR
  Hinske et al. Nat Genetics 2006

-----------------------------------------

- ACTN4 (alpha-actinin-4) - AD
  Kaplan et al, Nat Genetics 2000
- TRP6 (transient receptor potential cation channel 6) - AD
  Winn et al., Science 2005
  Reiser et al., Nat Genetics 2005
- INF2 (Formin)
  Pollak et al Nat Gen 2009 – AD
- ANLN (Anillin)
Which genetic mutations can be identified in adults with FSGS by whole exome sequencing?

Methods and Cohort

- Toronto GN Registry
- FSGS by kidney biopsy OR proteinuria + relative with FSGS
- N=193
  - 49% ESKD
  - 22% Familial FSGS

Whole Exome Sequencing

- COL4A3/4/5
  - Definitely pathogenic: 55%
  - Likely pathogenic: 39%

- Podocyte genes
  - Definitely pathogenic: 40%
  - Likely pathogenic: 33%

- CAKUT genes
  - Definitely pathogenic: 5%
  - Likely pathogenic: 17%

Conclusions: Even with an expanded gene panel, we find COL4A disorders are the leading monogenic cause in adults diagnosed with FSGS.

Fly-borne parasitic infection

Distribution of human African trypanosomiasis
(African sleeping sickness)

Number of reported cases, 2010
(T. gambiense)
- >1,000
- 100–1,000
- <100
- 0
- Endemic countries

Number of reported cases, 2010
(T. rhodesiense)
- ≥100
- <100
- 0
- Endemic countries
Apol1 G1 and G2 variants

Increased risk of non-diabetic kidney disease
- Especially FSGS and hypertensive disease

Resistance to Trypanosomiasis parasite
Kidney Transplant in FSGS
Steroid-Resistant Nephrotic Syndrome: Recurrence After Transplantation

LEOPOLDO RAIJ, M.D., JOHN R. HOYER, M.D., and ALFRED F. MICHAEL, M.D.,
Minneapolis, Minnesota
An appealing hypothesis is that a circulating humoral substance in these patients injures glomerular membranes, causing increased permeability to protein. The nature of such a factor(s) is not known. Careful clinical studies of patients with the idiopathic nephrotic syndrome after renal transplantation may throw light on the pathogenesis of this disorder.
Evidence for circulating factor in FSGS

- Transplant patients
  - Up to 30-40% recurrence post-transplant
  - Risk higher with subsequent transplants
  - Blood plasma from patients with recurrent FSGS can cause proteinuria in rats
Linking the understanding of the pathogenesis to treatment

Deegens et al. Kidney Int 2011
Existing validated targets?
<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Patient Diagnosis</th>
<th>Age Range</th>
<th>Drug/Compound</th>
<th>EGFR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aurora (Aurinia Pharmaceuticals, Inc.)</td>
<td>FSGS</td>
<td>18 - 75</td>
<td>Yocosporn</td>
<td>&gt;30</td>
</tr>
<tr>
<td>CCX140-B in Subjects with FSGS (ChemoCentryx, Inc.)</td>
<td>FSGS</td>
<td>18 - 75</td>
<td>CCX140-B</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Duplex (Retrophin, Inc.)</td>
<td>FSGS</td>
<td>8 – 75</td>
<td>Sparsentan</td>
<td>&gt;30</td>
</tr>
<tr>
<td>First (Complexa, Inc.)</td>
<td>FSGS</td>
<td>18+</td>
<td>CKA-10</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Podocyte Clinical Trial (Mallinckrodt Pharmaceuticals)</td>
<td>FSGS</td>
<td>18+</td>
<td>Acthar</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Trial to Evaluate PF-06730512 in Adults with FSGS (Pfizer Inc.)</td>
<td>FSGS</td>
<td>18 - 70</td>
<td>PF-06730512</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Abatacept to Reduce Proteinuria (Bristol-Myers Squibb Company)</td>
<td>Treatment Resistant FSGS or MCD</td>
<td>6 – 75</td>
<td>Abatacept</td>
<td>&gt;45</td>
</tr>
<tr>
<td>Efficacy &amp; Safety of Bieselumab to Prevent Recurrence (Astellas Pharma US, Inc.)</td>
<td>De novo transplant due to FSGS</td>
<td>18+</td>
<td>Bieselumab</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Conclusions

• It has been found that FSGS is a common underlying cause of renal disease
  – FSGS is the most common cause of idiopathic (unknown cause) nephrotic syndrome in USA
  – Most common primary glomerular disease underlying kidney failure in USA
  – Increasing in incidence for unclear reasons
Conclusions

• Apol1 mutations are highly associated with FSGS
• Genetics of podocytopathies becoming increasingly clinically relevant
• Evidence supports a central role for a circulating factor in FSGS
• Targeted therapy for podocyte dysfunction being pursued
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• How kidney donation affects the health of the donor
• Financial considerations for living donors

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