What is “Secondary” Focal Segmental Glomerulosclerosis?

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Brinkhous Distinguished Professor and Chair of Pathology and Laboratory Medicine
University of North Carolina at Chapel Hill

Theodor Fahr, 1925
What is “Secondary” Focal Segmental Glomerulosclerosis?

- Nephrotic syndrome pathology historical background
- Evolution of the pathologic concepts of FSGS
- Evolution of the concept of primary versus secondary FSGS
- The future of secondary FSGS
Nephrotic Syndrome:

Historical Background

• The relationship between severe edema (dropsy) and kidney disease was known to Greek and Arab physicians two thousand years ago.

• Although noted less definitively earlier by others, in 1827 Richard Bright documented the association between dropsy (edema), coagulable urine (albuminuria), and kidney disease. He also reported observations by Bostock of hypoalbuminemia and hyperlipidemia.

From Frederici Dekkers. Exercitationes practicae circa medendi methodum. Lugduni Batavorum: Apud Jordanum Luchtmans, Cornelium Boutesteyn, 1695. (Carl Gottschalk Rare Book Collection, UNC Library)
Nephrotic Syndrome: Historical Background

• In 1905, a German pathologists, Friedrich von Muller, introduced the term “nephrosis” for the apparently non-inflammatory causes of kidney disease to distinguish them from inflammatory “nephritis”.

• The clinical syndrome described by Bright and others merged with the pathologic term for associated lesions and became the “nephrotic syndrome”.

From Frederici Dekkers. Exercitationes practicae circa medendi methodum. Lugduni Batavorum: Apud Jordanum Luchtmans, Cornelium Boutesteyn, 1695. (Carl Gottschalk Rare Book Collection, UNC Library)

Theodor Fahr, in Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin. VI:121, 1925
In his 1925 treatise on renal pathology, Theodor Fahr included lipoid nephrosis, amyloidosis, eclampsia, and diabetes in the nephrosis category. He described a progressive form of “Lipoidnephrose” with “Hyalinisierung” and beautifully illustrated what today would be called focal segmental glomerulosclerosis.

Pathologische Anatomie des Morbus Brightii.

Von Fahr-Hamburg.

Handbuch der speziellen pathologischen Anatomie und Histologie. Berlin. VI:121, 1925
In 1957, Arnold Rich was the first to report the FSGS pattern of glomerular injury in detail in the English language literature, and observed a juxtamedullar predilection in his specimens.

**A HITHERTO UNDESCRIBED VULNERABILITY OF THE JUXTAMEDULLARY GLOMERULI IN LIPOID NEPHROSIS**

**ARNOLD R. RICH**

*The Department of Pathology, The Johns Hopkins University School of Medicine*


Described autopsy findings in 20 patients who presented with “pure lipoid nephrosis” and died from uremia or Pneumococcal peritonitis. Four had no glomerular sclerosis, 5 had sclerosis only in juxtamedullary glomeruli, 7 had more severe sclerotic lesions in juxtamedullary glomeruli, and 4 had glomerular sclerosis throughout the cortex.
In 1961, Habib and her colleagues reported the pathologic findings in children with “primary nephrotic syndrome,” i.e. not secondary to systemic disease.

CLINICAL, MICROSCOPIC AND ELECTRON MICROSCOPIC DATA IN THE NEPHROTIC SYNDROME OF UNKNOWN ORIGIN

R. HABIB, P. MICHIlsen, E. DE MONTERA, N. HINGLAIS, P. GALLE and J. HAMBURGER


It is partly due to renal biopsy that the concept of “lipoid nephrosis”, an autonomous disorder, has been replaced by the concept of nephrotic syndrome caused by renal changes of various origins and nature. Thus amyloidosis, lupus and diabetic glomerulosclerosis are today listed among the causes of nephrotic syndrome. For the majority of cases, however, no such aetiology has been established, and they are often designated as “primary nephrotic syndrome”. In this study we shall refer to them as “nephrotic syndrome of unknown origin”.
In this 1961 study of 108 children with “primary nephrotic syndrome”, Habib et al reported 5 patients with “irregular glomerular hyalinosis” that probably was FSGS.

<table>
<thead>
<tr>
<th>Main types of lesions</th>
<th>Number of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) Minimal changes</td>
<td>35</td>
</tr>
<tr>
<td>(2) Thickened capillary walls (or “membranous glomerulonephritis”)</td>
<td>19</td>
</tr>
<tr>
<td>(3) Extracapillary proliferative glomerulitis (focal or diffuse)</td>
<td>9</td>
</tr>
<tr>
<td>(4) Endocapillary proliferative glomerulitis</td>
<td>5</td>
</tr>
<tr>
<td>(5) Endocapillary proliferative glomerulitis associated with hyaline nodules (“lobular glomerulitis”)</td>
<td>15</td>
</tr>
<tr>
<td>(6) Complex or unclassifiable forms</td>
<td></td>
</tr>
<tr>
<td>(a) Irregular glomerular hyalinosis</td>
<td>5</td>
</tr>
<tr>
<td>(b) Thickened capillary walls with endocapillary proliferation</td>
<td>7</td>
</tr>
<tr>
<td>(c) Advanced forms which cannot be interpreted</td>
<td>13</td>
</tr>
</tbody>
</table>

In 1970, Churg, Habib and White reported “Focal Sclerosing Glomerular Lesions” in renal biopsies from 12 of 127 children with nephrotic syndrome.

“This group was characterized by the presence of glomerular sclerosis which was of both focal and segmental distribution.”

Lancet I:1299, 1970
35 of 406 had "Segmental and focal hyalinosis"

### TABLE 2. Anatomic Classification of Idiopathic Nephrotic Syndrome of Childhood (406 Cases)

<table>
<thead>
<tr>
<th>Classification</th>
<th>Total Cases</th>
<th>% of Total</th>
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<tbody>
<tr>
<td>I. Minimal glomerular lesions</td>
<td>209</td>
<td>51.5</td>
</tr>
<tr>
<td>II. Focal glomerular lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Segmental and focal hyalinosis</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>b. Global and focal glomerular fibrosis</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>III. Diffuse glomerular lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>a. Glomerulonephritis with extramembranous deposits</td>
<td>37</td>
<td>9</td>
</tr>
<tr>
<td>b. Proliferative glomerulonephritis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pure endocapillary</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>endo- and extracapillary</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>membranoproliferative</td>
<td>38</td>
<td>9</td>
</tr>
<tr>
<td>lobular</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>IV. &quot;Microcystic&quot; nephrotic syndrome</td>
<td>6</td>
<td>1.5</td>
</tr>
<tr>
<td>V. Unclassified glomerular lesions</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>TOTAL</td>
<td>406</td>
<td>100</td>
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</table>
In 1973, Hyman and Burkholder published a definitive detailed description of the pathologic and clinical features of FSGS 58 renal biopsies form 33 patients.

Focal Sclerosing Glomerulonephropathy with Segmental Hyalinosis

A Clinicopathologic Analysis

Lawrence R. Hyman, M.D., and Peter M. Burkholder, M.D.

Laboratory Investigation 28:533, 1973
# Causes of Nephrotic Syndrome in Heptinstall’s Pathology of the Kidney

<table>
<thead>
<tr>
<th></th>
<th></th>
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<tbody>
<tr>
<td>Glomerulonephritis</td>
<td>Glomerulonephritis</td>
<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Proliferative Membranous Lobular</td>
<td>Proliferative Membranous</td>
<td>Proliferative Membranous</td>
</tr>
<tr>
<td>Chronic Focal</td>
<td>Chronic Focal</td>
<td>Chronic Focal</td>
</tr>
<tr>
<td>Lipoid nephrosis*</td>
<td>Lipoid nephrosis</td>
<td>Lipoid nephrosis</td>
</tr>
<tr>
<td>Systemic disease</td>
<td>Focal glomerulosclerosis*</td>
<td>Focal segmental glomerulosclerosis*</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Systemic disease</td>
<td>Systemic disease</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>Diabetes mellitus</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>SLE</td>
<td>Amyloidosis</td>
<td>Amyloidosis</td>
</tr>
<tr>
<td>HSP</td>
<td>SLE</td>
<td>SLE</td>
</tr>
<tr>
<td>Toxins</td>
<td>HSP</td>
<td>HSP</td>
</tr>
<tr>
<td>Circulatory disturbances</td>
<td>Toxins</td>
<td>Therapeutic agents</td>
</tr>
<tr>
<td>Infections</td>
<td>Circulatory disturbances</td>
<td>Infections</td>
</tr>
<tr>
<td>Herdofamilial</td>
<td>Infections</td>
<td>Infantile or congenital</td>
</tr>
<tr>
<td>*Mentioned Rich’s observations in 4 lines of text</td>
<td>*5 pages of text on FSGS</td>
<td>*21 pages of text on FSGS</td>
</tr>
</tbody>
</table>
## Causes of Nephrotic Syndrome in Heptinstall’s Pathology of the Kidney

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Glomerulonephritis</td>
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<td>Glomerulonephritis</td>
</tr>
<tr>
<td>Proliferative</td>
<td>Proliferative</td>
<td>Proliferative</td>
</tr>
<tr>
<td>Membranous</td>
<td>Membranous</td>
<td>Membranous</td>
</tr>
<tr>
<td>Lobular</td>
<td>MPGN and Lobular</td>
<td>MPGN</td>
</tr>
<tr>
<td>Chronic</td>
<td>Chronic</td>
<td>Chronic</td>
</tr>
<tr>
<td>Focal</td>
<td>Focal</td>
<td>Focal</td>
</tr>
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<td>Systemic disease</td>
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</tr>
<tr>
<td>HSP</td>
<td></td>
<td>HSP</td>
</tr>
<tr>
<td>Toxins</td>
<td></td>
<td>Toxins</td>
</tr>
<tr>
<td>Circulatory</td>
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<tr>
<td>disturbances</td>
<td></td>
<td>disturbances</td>
</tr>
<tr>
<td>Infections</td>
<td></td>
<td>Infections</td>
</tr>
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<td></td>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No mention of secondary FSGS</td>
</tr>
</tbody>
</table>

*5 pages of text on FSGS

*21 pages of text on FSGS
Pathogenesis and Significance of Nonprimary Focal and Segmental Glomerulosclerosis


Primary alterations of podocytes

Idiopathic FSGS
HIV-associated nephropathy
Heroin-associated nephropathy

Secondary to structural and/or functional adaptations with reduced numbers of functioning nephrons

Unilateral renal agenesis
Oliomeganephronia
Renal dysplasia
Adult PKD
Reflux nephropathy
Chronic interstitial nephritis
Partial cortical necrosis
Papillary necrosis
Sickle cell disease
Surgical ablation
Primary glomerulopathies

Secondary to structural and/or functional adaptations initially with normal numbers of nephrons

Diabetic nephropathy
Glycogen storage disease
Familial dysautonomia
Morbid obesity
Congenital cyanotic heart defects

Secondary to hereditary GBM defects

Hereditary nephritis
Nail-patella syndrome

Secondary to focal proliferative glomerulonephritides
### Types of FSGS Listed in Heptinstall’s Pathology of the Kidney 5th ed, 1998

<table>
<thead>
<tr>
<th>Primary (idiopathic) FSGS</th>
<th>Secondary FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Secondary</td>
</tr>
<tr>
<td>(idiopathic) FSGS</td>
<td>Focal proliferative GN</td>
</tr>
<tr>
<td>Collapsing glomerulopathy</td>
<td>Alport’s syndrome</td>
</tr>
<tr>
<td>Cellular variant</td>
<td>Hypertension</td>
</tr>
<tr>
<td>Glomerular tip lesion</td>
<td>Membranous GN</td>
</tr>
<tr>
<td>FSGS with reduced renal mass</td>
<td>Glycogen storage disease</td>
</tr>
<tr>
<td>Reflux nephropathy</td>
<td>Sickle cell disease</td>
</tr>
<tr>
<td>Dysplasia</td>
<td>Preeclampsia</td>
</tr>
<tr>
<td>Oligomeganephronia</td>
<td>Diabetes</td>
</tr>
<tr>
<td>Unilateral renal agenesis</td>
<td>HIV-associated FSGS</td>
</tr>
<tr>
<td>Morbid obesity</td>
<td>Heroin-associated FSGS</td>
</tr>
<tr>
<td>Failing allograft</td>
<td></td>
</tr>
<tr>
<td>Renovascular disease</td>
<td></td>
</tr>
</tbody>
</table>

Types of FSGS Listed in Heptinstall’s Pathology of the Kidney
5th ed, 1998

**Primary (idiopathic) FSGS**
- Collapsing glomerulopathy
- Cellular variant
- Glomerular tip lesion

**Secondary FSGS**
- Focal proliferative GN
- Alport’s syndrome
- Hypertension
- Membranous GN
- Glycogen storage disease
- Sickle cell disease
- Preeclampsia
- Diabetes

**FSGS with reduced renal mass**
- Reflux nephropathy
- Dysplasia
- Oligomeganephronia
- Unilateral renal agenesis
- Morbid obesity
- Failing allograft
- Renovascular disease

**HIV-associated FSGS**
**Heroin-associated FSGS**

Over the past 10 years, the elucidation of genetic abnormalities in podocyte proteins that can lead to FSGS has resulted in a still expanding list genetically determined causes for FSGS.

Alpha actinin 4
Beta 4 integrin
CD2AP
Laminin beta 2
mtMTTL1
Nephrin
Podocin
PLCE1
SMARCAL1
Tetraspanin 24
TRAPC 6
WT-1
Etc.

Wilhelm Kritz, 2005

**Primary (idiopathic) FSGS**

**Secondary FSGS**

1. Familial/genetic
   - A. Mutations in α-actinin 4
   - B. Mutations in podocin
   - C. Mutations in WT-1
   - D. Mutations in β integrin

2. Virus-associated
   - A. HIV-1
   - B. Parvovirus B19

3. Drug-induced
   - A. Heroin
   - B. Interferon-α
   - C. Lithium
   - D. Pamidronate

4. Mediated by adaptive structural-functional responses
   - A. Reduced renal mass
   - B. Initially normal renal mass

A. Reduced renal mass
   - Oligomeganephronia
   - Unilateral renal agenesis
   - Renal dysplasia
   - Reflux nephropathy
   - Sequela to cortical necrosis
   - Surgical renal ablation
   - Chronic allograft nephropathy
   - Any advanced renal disease

B. Initially normal renal mass
   - Hypertension
   - Atheroemboli
   - Obesity
   - Cyanotic congenital heart disease
   - Sickle cell anemia
Causes of FSGS Listed in Heptinstall’s Pathology of the Kidney
6th ed, 2007

Podocyte injury, unknown cause
Primary FSGS

Podocyte injury, defined cause
Viral
HIVAN
Parvovirus B19
Drugs
Interferon-α
Pamidronate
Lithium

Secondary to structural and/or functional adaptations
With reduced functioning nephrons
Unilateral renal agenesis
Oligomeganehronia and hypoplasia
Renal dysplasia
Polycystic kidney disease, adult type
Reflux nephropathy
Chronic interstitial nephritis & pyelonephritis
Partial cortical necrosis
Papillary necrosis (analgesic nephropathy)
Sickle cell disease
Primary glomerulopathies
Extensive surgical ablation
Cholesterol atheroembolization
Hypertension

Initially with normal number of nephrons
Morbid obesity
Cyanotic congenital heart disease
Diabetic nephropathy
Glycogen storage diseases
Familial dysautonomia
Acromegaly

Secondary to genetic diseases
Autosomal recessive FSGS
Nephrin (NPHS1) mutations
Podocin (NPHS2) mutations

Autosomal dominant FSGS
Localized to 11q21–22
α-actinin-4 mutations
Others
CD2AP mutations

Syndromic FSGS

MT1 mutations
Diffuse mesangial sclerosis
Denys-Drash syndrome
Frasier syndrome
Nail-patella syndrome
Alport’s syndrome
Galloway Mowat syndrome
AD FSGS and sensorineural deafness
AR FSGS eurologic findings

Mitochondrial DNA mutations (mtMTTL1)
MELAS syndrome
Deafness and diabetes mellitus

Secondary to focal glomerulonephritides

Schwartz MM: Focal Segmental Glomerulosclerosis in Heptinstall’s Pathology of the Kidney, 6th Edition,
Jennette JC, Olson JL, Schwartz MM, Silva FG (eds),
Lippincott Williams & Wilkins, Philadelphia, 2007,
Chapter 5, 155-204
## Causes of FSGS Listed in Heptinstall’s Pathology of the Kidney
6th ed, 2007

### Secondary to genetic diseases

#### Autosomal recessive FSGS
- Nephrin (NPHS1) mutations
- Podocin (NPHS2) mutations

#### Autosomal dominant FSGS
- Localized to 11q21–22
- α-actinin-4 mutations
- Others

#### CD2AP mutations

#### Syndromic FSGS
- WT1 mutations
  - Diffuse mesangial sclerosis
  - Denys-Drash syndrome
- Frasier syndrome
- Nail-patella syndrome
- Alport’s syndrome
- Galloway Mowat syndrome
- AD FSGS and sensorineural deafness
- AR FSGS eurologic findings

#### Mitochondrial DNA mutations (mtMTTL1)
- MELAS syndrome
- Deafness and diabetes mellitus

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Proposed 5 histopathologic categories of FSGS:

FSGS, not otherwise specified (NOS)

FSGS, perihilar variant

FSGS, cellular variant

FSGS, tip variant

FSGS, collapsing variant
Structural patterns of injury correlate with clinical presentations and outcomes.


### Etiology/Pathogenesis

<table>
<thead>
<tr>
<th>Primary (idiopathic) FSGS</th>
<th>Secondary FSGS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Familial/genetic</strong></td>
<td></td>
</tr>
<tr>
<td>A. Mutations in α-actinin 4</td>
<td>NOS, Perihilar, Tip, Cellular, Collapsing</td>
</tr>
<tr>
<td>B. Mutations in podocin</td>
<td>NOS, Perihilar, Collapsing</td>
</tr>
<tr>
<td>C. Mutations in WT-1</td>
<td></td>
</tr>
<tr>
<td>D. Mutations in β integrin</td>
<td></td>
</tr>
<tr>
<td><strong>2. Virus-associated</strong></td>
<td></td>
</tr>
<tr>
<td>A. HIV-1</td>
<td>Collapsing</td>
</tr>
<tr>
<td>B. Parvovirus B19</td>
<td>Collapsing</td>
</tr>
<tr>
<td><strong>3. Drug-induced</strong></td>
<td></td>
</tr>
<tr>
<td>A. Heroin</td>
<td>NOS, Perihilar &gt; NOS</td>
</tr>
<tr>
<td>B. Interferon-α</td>
<td>Perihilar &gt; NOS</td>
</tr>
<tr>
<td>C. Lithium</td>
<td></td>
</tr>
<tr>
<td>D. Pamidronate</td>
<td></td>
</tr>
<tr>
<td><strong>4. Mediated by adaptive structural-functional responses</strong></td>
<td></td>
</tr>
<tr>
<td>A. Reduced renal mass</td>
<td></td>
</tr>
<tr>
<td>B. Initially normal renal mass</td>
<td></td>
</tr>
</tbody>
</table>
Structural patterns of injury correlate with etiology and pathogenesis.


Average foot process width differs in different causes for nephrotic syndrome.
Structural patterns of injury correlate with etiology and pathogenesis.

Average foot process width differs in different causes for nephrotic syndrome.

Secondary to “maladaptive responses”

Structural patterns of injury correlate with etiology and pathogenesis

Average foot process width differs in different causes for nephrotic syndrome

Structural patterns of injury correlate with etiology and pathogenesis.

Average foot process width does not correlate with severity of proteinuria.

What is “Secondary” Focal Segmental Glomerulosclerosis?

**Primary**/idiopathic FSGS is FSGS of unknown cause.  
**Secondary** FSGS is FSGS secondary to a known cause.

Theodor Fahr, 1925
Etiologic Classification of FSGS

• Idiopathic (Primary) FSGS (unknown cause)
• FSGS secondary to intrinsic glomerular abnormalities
  • Genetic podocytopathies (e.g. mutations in genes for α-actinin 4, podocin, nephrin, TRPC6, PLCE1, WT-1, etc.)
  • Genetic mitochondriopathies (e.g. mutations in genes for tRNA Leu, COQ2, etc.)
  • Genetic basement membrane nephropathies (e.g. mutations in genes for type IV collagen chains, etc.)
• FSGS secondary to extrinsic factors that injure glomeruli
  • Obesity
  • Reduced renal mass caused by congenital disease, surgery, or acquired parenchymal disease
  • Aberrant oxygen delivery to the kidney: e.g. cyanotic congenital heart disease, sickle cell anemia, etc.
• Glomerular infections: e.g. HIV, parvovirus B-19, etc.
• Drug toxicity: e.g. pamidronate, heroin, interferon-α, lithium, etc.
All FSGS is secondary to structural and functional abnormalities. Primary (idiopathic) FSGS becomes secondary FSGS over time.