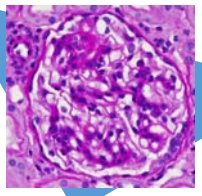
What's New in Pediatric FSGS?

Annual Dialysis Conference
Long Beach, March 11, 2017



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Changing the face of healthcare, one child at a time.

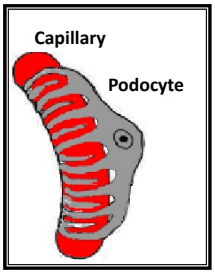
BEST CHILDREN'S HOSPITALS U.S. NEWS

Aims

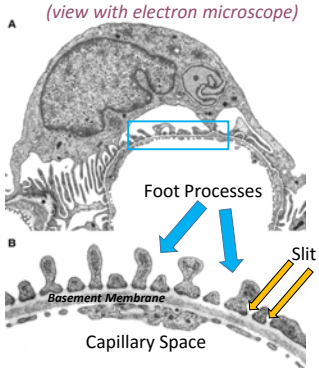
- Review glomerular podocyte biology and how it relates to FSGS
- Understand primary FSGS in childhood compared to
  - Genetic FSGS
  - Secondary FSGS in pediatrics
- Discuss current therapy and management of FSGS, including dialysis and kidney transplant

What's a Podocyte?

Glomerular Cell around the Capillary Loop with Interdigitating Foot Processes

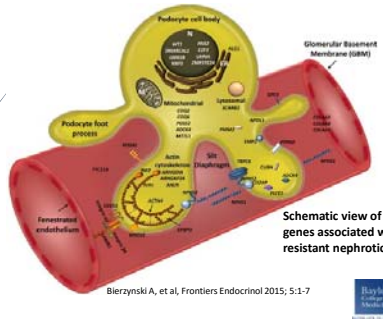


Normal Glomerular Podocyte
(view with electron microscope)



Pavenstadt H, Kriz W, Kretzler M, Physiol Rev 2003;83:253-307

Glomerular Podocyte Regulatory Function: Lots of Genes and their Gene Products Control What Gets Filtered into the Urine

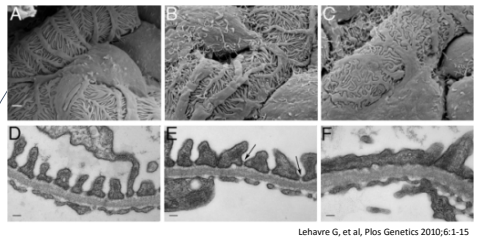


Schematic view of podocyte genes associated with steroid resistant nephrotic syndrome

Bierzynski A, et al, Frontiers Endocrinol 2015; 5:1-7

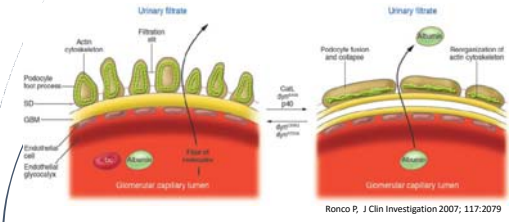
Progressive Foot Process (FP) Disorganization and Effacement Health → Disease*

Effacement =obliteration of form or features; the medical process of becoming shorter, thinner, softer like cervix in labor



Lehavre G, et al, Plos Genetics 2010;6:1-15

Diseased Podocytes/Effaced Foot Processes Lose their Complicated Endocytosis Function → Large Amounts Albumin Escape into Urine



Ronco P, J Clin Investigation 2007; 117:2079

How Do Podocytes Relate to FSGS?

- Normal podocytes help maintain the glomerular filtration barrier through complex interactions and signaling
- Podocytes adapt to stress & pathologic stimuli
- Excessive stress may lead to transient or permanent podocyte injury with loss of cell integrity and dysregulation of metabolism
  - "Sick podocytes"
    - Don't cross-talk well with capillary endothelial cells
    - May detach from GBM and undergo death/sclerosis
    - Limited podocyte capacity to replicate & cover gaps
    - One podocyte cell death/sclerosis → potential domino effect on other podocytes

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Pediatric FSGS

- Much less common cause of NS (~10%) than minimal change disease (~80%) in <10 yo
  - Usually not biopsied at presentation with NS
    - Unless high BP, serum Cr, gross hematuria or renal tubular disease (e.g. renal glucosuria)
  - Initial treatment FSGS same as for MCNS
- NS or proteinuria often poorly responsive or resistant to steroid therapy →then biopsy
- 50% of patients reach ESRD within 10 years
- Worse prognosis in adolescents, African Americans and Hispanics

Presentation of FSGS in Childhood-1

- Nephrotic syndrome (NS)
  - most frequent presentation
  - occurs in all pediatric age groups
    - about 10% of all 1-10 yo with NS
    - about 20% of all adolescents with NS
- Proteinuria alone
  - detected by screening urinalysis
- Up to 50% may have hematuria

Presentation of FSGS in Childhood-2

- Persistent or gross hematuria with NS suggests disease other than minimal change NS (MCNS)
  - ***FSGS***
  - *Membranoproliferative GN*
  - *Membranous GN*
  - *IgA nephropathy*
  - *Lupus nephritis*
- ***TRANSIENT*** *microscopic hematuria occurs in up to 25% with minimal change disease*

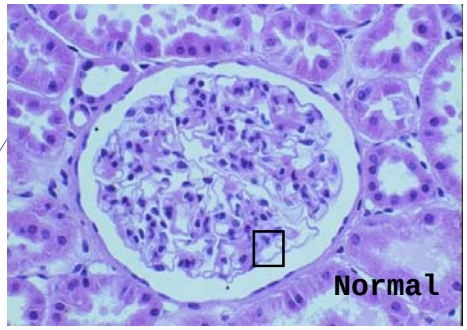
Presentation of FSGS in Childhood-3

- 4 criteria for diagnosis of nephrotic syndrome
  - Proteinuria
  - Hypoproteinemia
  - Edema (when serum albumin <2.5 g/dL)
  - Hyperlipidemia (serum cholesterol, triglycerides)
- Nephrotic range proteinuria, if no edema
  - *random urine protein/creatinine ratio >2 mg/mg*
  - *24-hour urine protein >40 mg/m^2 BSA/hr (>1700 mg/1.73m^2 BSA/day)*

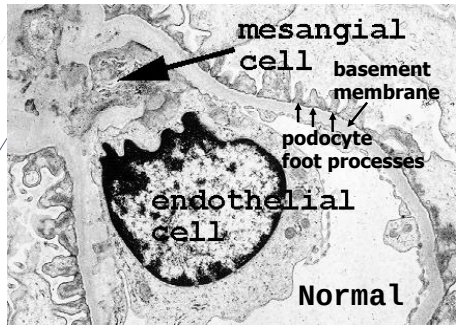
Pediatric FSGS: Diagnosis

- Suspect if poor response to initial steroids
  - Resistance to 8 week course high-dose corticosteroids
  - Frequently relapsing NS with taper of corticosteroids
- Renal biopsy needed for diagnosis
  - Indicated before 8 weeks corticosteroid therapy, if
    - Hypertension
    - Renal failure
    - Gross hematuria ± red blood cell casts
    - Presentation between 3-12 months of age
    - Presentation as adolescent
    - Positive family history for FSGS

Normal Kidney Biopsy: Light Microscopy



Normal Kidney Biopsy: Electron Microscopy



Pathology of FSGS Kidney Biopsy

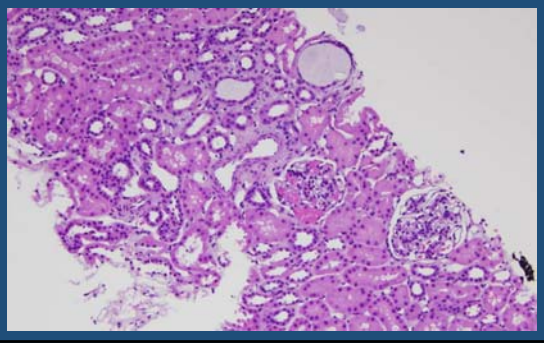
- **Focal:** affects only some glomeruli
  - opposite = diffuse (affects all of the glomeruli)
  - glomeruli at corticomedullary junction affected first
- **Segmental:** affects only part of glomerulus
  - opposite = global (affects the whole glomerulus)
- Pathologist does serial examination of the entire renal biopsy core to look for the focal lesions
  - Earliest lesions in glomeruli at corticomedullary junction
- Key lesion: segmental sclerosis or hyalinosis
- Glomerular tip lesion (earliest lesion)
  - prominent vacuolated podocytes & intracapillary foam cells at/adjacent to urinary pole of glomerulus; often with adhesion to Bowman's capsule

Pathology of FSGS Kidney Biopsy: Columbia Classification (2004)

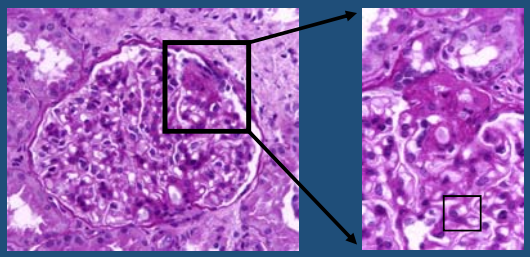
Type	Key Histology	Possible Prognosis
Not otherwise specified	Segmental sclerosis	Typical Course
Tip lesion	Sclerosis of glomerular tuft at proximal (urinary) pole	Better prognosis? Early lesion?
Cellular	Endocapillary proliferation, often podocyte hyperplasia	Early lesion?
Collapsing	Collapse of glomerular tuft, podocyte hyperplasia	**Poor**
Perihilar	Sclerosis and hyalinosis at glomerular vascular pole	Secondary FSGS?

Adapted from Fogo A, Nat Rev Nephrol 2015; 11:76-87

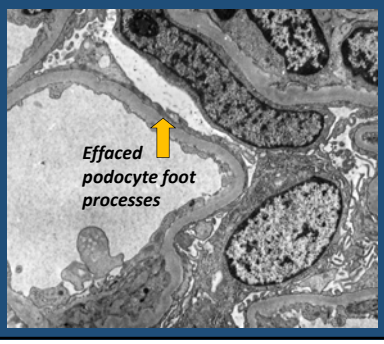
FSGS Kidney Biopsy:
Light Microscopy (PAS Stain)



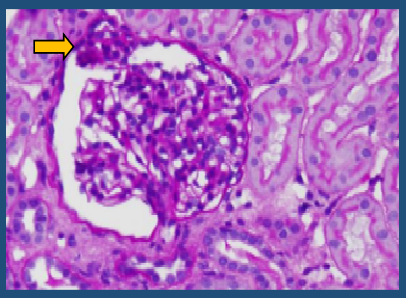
FSGS Kidney Biopsy-single glomerulus:
Light Microscopy (PAS Stain)



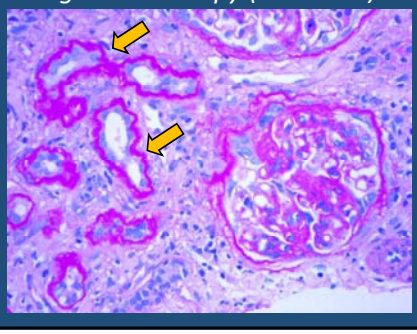
FSGS Kidney Biopsy:
Electron Microscopy (EM)



FSGS Kidney Biopsy-Tip Lesion: Light Microscopy (PAS Stain)



FSGS Kidney Biopsy-Advanced with Tubular Atrophy & Fibrosis: Light Microscopy (PAS Stain)



Pediatric FSGS

- Primary FSGS
  - No identifiable associated disease or toxin
  - Most common cause of ESRD resulting from primary childhood NS or glomerulonephritis
- Genetic FSGS (including familial FSGS)
- Secondary NS/FSGS
  - Presence of other systemic disease (like lupus, HSP), hereditary disease, infections, or drugs/toxins

Pediatric Secondary NS/FSGS: Causes

Hereditary Diseases

- Familial FSGS (NPHS2 podicin mutation)
- Denys-Drash syndrome
- Congenital NS, Finnish type
- Congenital NS, mesangial sclerosis
- Schimke immunoosseous dysplasia
- Nail-patella syndrome
- Alport's hereditary nephritis
- Galloway-Mowat syndrome
- Charcot-Marie Tooth disease
- Jeune's syndrome
- Bardet-Biedl syndrome
- Lipoprotein disorders

- ***Infections***
  - HIV nephropathy
  - Malaria
  - Hepatitis B
  - Syphylis, CMV, toxoplasma
- ***Drugs/Toxins***
  - Penicillamine, gold
  - NSAIDS
  - Mercury, lithium
  - Sirolimus
- ***Malignancy***
  - Lymphoma, leukemia
- ***Glom hyperfiltration***
  - Morbid obesity
  - Adaptation to ↓kidney tissue (small BW babies)

Pediatric Genetic FSGS

- Accounts for about 20% of FSGS in childhood
- About 70% present with NS in first 2 years of life, so genetic FSGS should always be considered in steroid-resistant NS in <3yo
  - Diagnosis FSGS by kidney biopsy
  - Whole blood for "early onset genetic evaluation for nephrotic syndrome"
    - 2 mL (ped, minimum 1 mL) or 8 mL (adult) sample (Athena Diagnostics; results turn around in 2-4 wks)
    - Currently detects mutations in NPHS1, NPHS2, PLCE1, LAMB2, and WT1 genes

Genes Associated with Pediatric NS/FSGS

(PC=podocyte; AR=autosomal recessive; AD=autosomal dominant)

Gene	Protein Product	Function	Presentation
NPHS1*	Nephrin	PC slit diaphragm	Congenital NS
NPHS2*	Podocin	PC slit diaphragm	Early onset AR-FSGS
MYO1E	Unconventional myosin 1E	Actin function	Early onset AR-FSGS
ARHGDIA	Rho GDP-dissociation inhibitor 1	Rho GTPase signaling, actin dynamics	Early onset AR-FSGS
PLCE1*	Phospholipase Cε1	PC differentiation	Early onset AR-FSGS
CD151	CD151 antigen	PC, GBM laminating integrin interaction	Early onset AR-FSGS
PTPRO	Receptor-type tyrosine protein phosphatase O	PC signaling	Childhood AR-FSGS
SMARCAL1	SWI/SNF-related matrix associated regulator…	Chromatin bundling, gene transcription	Childhood FSGS,AR-Shimke
LAMB2*	Laminin B2 chain	Interacts with integrin, cytoskeleton	FSGS, AR-Pierson syndrome
ITGB4	Integrin β4	Cell-matrix adhesion	Rare FSGS
WT1*	Wilms tumor protein	PC development	Sporadic AD-FSGS

*Whole blood gene mutation analysis available

Adapted from Fogo A, Nat Rev Nephrol 2015; 11:76-87

Pediatric Primary FSGS

- Most common type of FSGS in childhood (80%)
- Increased incidence in African-Americans
  - 2-3x higher in adult primary FSGS; ***APOL1 gene***-associated
- 90% present with nephrotic syndrome
- Caused by primary podocyte problem(s)
- Recurs in kidney transplant
- Search for biomarkers (examples) for diagnosis
  - SuPAR: Soluble urokinase plasminogen activating receptor in blood or urine proposed as biomarker, but never confirmed
  - CD80 staining of podocytes→ not specific for primary FSGS *vs.* secondary FSGS or minimal change NS

Primary FSGS Pathogenesis

- Likely multifactorial
  - Podocyte injury?
    - Gene mutations of podocyte proteins of slit diaphragm disrupt interaction with glomerular basement membrane, lead to urine protein loss →fibrosis →podocyte cell death
  - Circulating "permeability" factor? NS recurs within hours of renal transplant before histologic changes on biopsy
  - Immune dysregulation?
    - Infectious agents (like HIV)
    - Abnormal T-cells (lymphoma)
- Understanding normal structure/function of podocytes key to new insights into FSGS pathogenesis
- Understanding pathogenesis should be focus to find better therapy for FSGS

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Pediatric FSGS Therapy-1

Initial Therapy—Corticosteroids

- Trial 8 weeks high-dose corticosteroids
  - Prednisone 2 mg/kg/day or 60 mg/m^2/day
  - Give daily for 4 weeks, then every other day for 4 weeks if no response
  - Taper when urine protein negative or trace for several consecutive days
- ***Rationale:*** empiric; steroids also known to affect podocytes

No clear guide to best steroid dosing or next drug therapy

- Randomized clinical trials to date show no next drug regimen superior to others

Pediatric FSGS Therapy-2

Historical

- **Alkylating agents** (cyclophosphamide)
  - 1984: 30% steroid unresponsive patients responded
  - 1996 (ISKD): remission rate same in steroid *vs.* steroid+cyclophosphamide treated (25-30%)
- **High dose IV pulse methylprednisolone**
  - With or without alkylating agent (Tune-Mendoza protocol)
  - Response in >50%; complete remission off drug in some
  - No randomized prospective clinical trials
  - Complications: severe infections, steroid side-effects
  - Mostly Caucasian patients; uncertain if as effective in African Americans and Hispanics

Pediatric FSGS Therapy-3

Calcineurin inhibitors (CNI)

- **Cyclosporine** (common choice)
  - Efficacy: 45-75% partial or complete NS remission; high relapse rate within 6 mon or more after stoppin
- **Tacrolimus** (few studies)
- ***Rationale***
  - Calcineurin expressed in podocytes
  - CNI reduces podocyte injury by restoring some podocyte-specific proteins and decreasing intracellular calcium influx to stabilize actin cytoskeleton in stressed podocyte
  - Animal studies show effects independent of immunologic effects of CNI on activated T-cells
- Nephrotoxic

Pediatric FSGS Therapy-4

Mycophenolate mofetil (MMF)

- Efficacy: 30-40%, partial or complete
  - No better than CNI
    (NIH randomized clinical trial FSGS in children and young adults; Gipson et al, Kidney International 2011; 80:868-878)
- ***Rationale:*** empiric

Pediatric FSGS Therapy-5

Renin-angiotensin system (RAS) inhibitors

- Well known drugs to treat ped hypertension
  - ACE-I =angiotensin-converting enzyme inhibitor: lisinopril, enalapril, etc
  - ARB =angiotensin receptor blocker: losartan, etc
- Used historically in FSGS for supportive care to
  - Decrease proteinuria
  - Prevent glomerular fibrosis
- ***New Rationale:*** inhibition of injured podocyte RAS signaling may reduce injury

Pediatric FSGS Therapy-6

Newer drugs

- **IV rituximab**
  - Chimeric monoclonal antibody against CD20 glycoprotein found on B-cells
  - Few studies; response in 20-30% FSGS; used after transplant
  - ***Rationale:*** also known to target podocyte cytoskeleton
- **IV abatacept**
  - Inhibitor of costimulatory modulator B7-1 found in T-cells and podocytes; used in kidney transplants
  - Few studies of primary and recurrent FSGS
  - ***Rationale:*** decrease in podocyte B7-1 may prevent actin cytoskeleton destabilization→ decreased FP effacement and proteinuria

FSGS Recurrence in Transplant

Pediatric recurrence rate as high as 55%

- NS may recur in few hours after transplant when no histologic changes on biopsy
- If recurrence, 2nd transplant recurrence rate as high as 85%
- Lower incidence of recurrence in African-American *vs.* Caucasian, Hispanic, Asian
- Low risk of recurrence of genetic FSGS

FSGS Recurrence in Transplant

- Chronic dialysis for 1 year before transplant may decrease risk
- Treatment of recurrence
  - Pre-transplant (TX) pheresis?
  - Steroids and cyclosporine
  - Post-TX early, frequent plasmapheresis
    - more effective in younger children than adolescents
  - IV rituximab; IV abatacept

Pediatric FSGS Summary

- Usually presents as primary nephrotic syndrome
- Not the most common cause of NS (~10-20%), but ***THE*** most common cause of NS leading to pediatric ESRD
  - Usually after 5-10 years
  - ~15% all ESRD pts, 40% of all those with GN
- Worse prognosis: African-American, Hispanic, adolescent
- Transplant recurrence rate for primary FSGS up to 55%
- Better understanding of pathogenesis is to key to improving therapy
- Knowledge of podocyte biology and genetic mutations is leading to new insight

STAY TUNED