

# PROTEINURIA IN CHILDREN

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# A CASE

- 15 year old girl presents for a sports physical
- Found to have a U/A with:
  - 1015/5/no blood/no sugar/no LE/no nitrites  
**100 mg/dL protein**

# MECHANISMS OF PROTEINURIA

- GLOMERULAR
  - FEVER/EXERCISE/ORTHOSTATIC
  - GLOMERULAR DISEASE
- TUBULAR
  - LMW PROTEINS
  - TUBULOINTERSTITIAL DISEASE
  - FANCONI'S SYNDROME
- OVERFLOW PROTEINURIA

# SYMPTOMATIC OR ASYMPTOMATIC PROTEINURIA?

- History:
  - swelling, gross hematuria
  - joint pains, rashes
  - previous UTIs
- Physical:
  - growth
  - blood pressure
  - edema

Our case: entirely asymptomatic  
with a benign exam. She has  
never had a UTI.

# HOW COMMON IS PROTEINURIA?

- 5-10% OF CHILDREN WILL HAVE  
1+ OR GREATER
- 0.1% WILL HAVE PERSISTENT  
PROTEINURIA

# IS THE PROTEINURIA REAL?

- Remember that the urine dipsticks only measure concentration.
- Evaluate urine protein/Cr ratio on a spot urine sample (normal  $<0.2$ )
- 24 hour urine collection

# IS THE PROTEINURIA DANGEROUS?

If the proteinuria is transient or orthostatic,  
it is benign.



# EVALUATE FOR ORTHOSTATIC PROTEINURIA

**\*\*Give patient urine collection cup to take home.\*\*\***

- Void before bed
- Upon awakening: quick sitz bath
- collect mid void sample
- refrigerate sample
- send for U/A and urine pro/cr

# INTERPRETING THE FIRST AM VOID

- If the first AM void shows normal protein excretion, no further work-up is needed.
- If the first AM void is abnormal (urine pro/cr ratio  $>0.2$ ):
  - Repeat directions
  - Repeat sample

# ASYMPTOMATIC PROTEINURIA

If proteinuria is persistent and not orthostatic:

**REFER TO A NEPHROLOGIST!!**

# DIFFERENTIAL DIAGNOSIS OF ASYMPTOMATIC PROTEINURIA

- Focal Segmental Glomerulosclerosis
  - FSGS
- Reflux Nephropathy
- Glomerulonephritis
- Systemic Lupus Erythematosus

# ASYMPTOMATIC PROTEINURIA: WHAT IT IS NOT.

- It is absolutely not Minimal Change Nephrotic Syndrome
- There is no indication for a steroid trial.

# ASYMPTOMATIC PROTEINURIA: WORK-UP

- Renal function
- \*\*\*Albumin\*\*\*
- Glomerulonephritis work-up:
  - C3, C4, CH50,
  - Hepatitis B
  - ANA, ds DNA, ?ANCA
- Renal ultrasound
- ?DMSA scan

# NONNORTHOSTATIC ASYMPTOMATIC PROTEINURIA

- Important to make a definitive diagnosis
- Renal Biopsy may be indicated.

# FOCAL SEGMENTAL GLOMERULOSCLEROSIS

- Some parts of some glomeruli have scars
- Frequently presents as nephrotic syndrome
- May present as asymptomatic proteinuria
- High incidence of progression to renal failure



# FSGS

- Hyperfiltration
  - Reduced renal mass
  - Hypertension
  - Diabetes Mellitus
  - Sickle Cell Nephropathy
- Immune mediated

# FSGS: TREATMENT

- Hyperfiltration
  - ACE inhibitors
  - ARB
- Immune mediated
  - Solumedrol
  - Calcineurin inhibitors
  - Mycophenylate

# REFLUX NEPHROPATHY

- Renal scarring related to UTIs in association with vesicoureteral reflux.
- If bilateral, may cause renal failure
- If unilateral may cause asymptomatic proteinuria and hypertension.

# REFLUX NEPHROPATHY: DIAGNOSIS

- DMSA Scan
- Consider even if there is not a clear history of UTIs
- Unilateral scarring may result in asymmetry of renal lengths on renal ultrasound

# SCREENING U/As

- The only way to detect asymptomatic proteinuria
- Cost effectiveness?
  - Screen first AM void
  - Try to avoid unnecessary testing or referrals.

# SYMPTOMATIC PROTEINURIA

- Symptoms/signs of glomerulonephritis
  - gross hematuria
  - hypertension
  - renal insufficiency
- Nephrotic syndrome

We will focus on Nephrotic  
Syndrome.

# A CASE

Three year old boy with swelling



# HISTORY

- Previously healthy
- URI 2-3 weeks ago
- Noted periorbital swelling one week ago
  - Dx: Allergies

# THE CASE CONTINUES

- Swelling worsens and now involves his entire body
- Diarrhea

# PHYSICAL EXAM

- BP= 100/50                      AF
- Marked periorbital edema
- Breath sounds clear but decreased at the bases
- Ascites, but nontender abdomen
- 3+ pitting edema to thigh
- Moderate scrotal edema

# WORK-UP

## Urinalysis:

- Yellow
- s.g.= 1030
- glu=neg
- ket=neg
- bld=small
- protein=neg
- nitrites=neg

## Micro:

15-20 RBC

0 WBC

3-5 Granular casts

# FURTHER WORK-UP

## BLOOD:

BUN=30

Alb=1.5

Cr=0.5

Chol=360

Na=131

Trig=300

K=3.8

Cl=115

Bicarb=24

# MORE URINE STUDIES

- Urine pro/cr ratio=15
  - $>10$  is considered nephrotic range proteinuria
- You consider a 24 hour urine collection but decide against it.
  - Greater than 1000 mg/M2 is considered nephrotic range proteinuria

# CXR

- Important to consider in child with anasarca
- Risk of pleural effusions
- Extremely unusual to see pulmonary edema with nephrotic syndrome, unless:
  - renal insufficiency
  - overly aggressive management with 25% albumin

# NEPHROTIC SYNDROME

- Criteria for diagnosis:
  - Edema
  - Nephrotic Range Proteinuria
  - Hypoalbuminemia
  - Hyperlipidemia



# HOW YOU COULD BE FOOLED

- Hypoalbuminemia without significant proteinuria:
  - Protein losing enteropathy
  - Decreased albumin synthesis
  - Lymphedema

# WHAT GIVES YOU NEPHROTIC SYNDROME IN A TODDLER?

- Minimal Change Disease
- Minimal Change Disease
- Minimal Change Disease
- Focal Segmental Glomerulosclerosis
- Membranous
- Membranoproliferative GN

# HOW TO BE EVEN MORE SURE THAT THIS IS MCNS

- Sudden presentation
- Normal blood pressure
- No hematuria
  - Hematuria in 25% with MCNS
- Normal Creatinine
- Normal Complement levels
- Steroid responsiveness

# OTHER BLOOD WORK TO BE DONE AT PRESENTATION

- Complement levels
- ANA
- Check on varicella status

# IT IS NOT MINIMAL CHANGE DISEASE WHEN:

- Presentation as an infant
- Asymptomatic proteinuria
- Low complement levels
- Be suspicious in teenagers

# SO WHAT IS MCNS?

- Minimally altered glomerular structure
- Fusion of podocytes
- Profound proteinuria
- Steroid responsiveness
- Relapsing course
- Can be outgrown

# NEPHROTIC SYNDROME IN CHILDREN IS CHANGING

- Incidence of FSGS is on the rise
- Dramatic increase of around 300% since the 1960's
- FSGS is much more prevalent in African Americans

# FOCAL SEGMENTAL GLOMERULOSCLEROSIS

- Histologic Diagnosis
- More likely to be steroid resistant
- May present as asymptomatic proteinuria
- Higher chance of progression to renal failure



# INCREASED INCIDENCE OF FSGS

??Related to the obesity epidemic??

Obesity induced FSGS

Hypertension induced FSGS

# OUR CASE

- We assume our patient has minimal change disease...
  - No need for a renal biopsy
- Now what do we do?

# TREATMENT OF NEPHROTIC SYNDROME

- Control the edema
- Prevent complications
- Stop the proteinuria
- Minimize medication side effects

# WHY DO YOU GET EDEMATOUS?

- Starling equilibrium
- 80% of oncotic pressure is due to albumin
- With albumin less than 2.5 mg/dL edema forms
- Albumin infusions as treatment

# GENERAL MEASURE

- Diet: Low salt
- Fluid restriction
- Diuretics?

# NUTRITIONAL ADVICE

- No added salt
- No fast food
- No food in little plastic packets
- Limit milk and cheese
- 2 gm/day

# DIURETICS

- Very tempting but potentially dangerous
  - Potentiates intravascular depletion
  - Increases risk of ATN
  - Increases risk of thrombosis

# COMPLICATIONS FROM EDEMA

- Spontaneous Peritonitis
- Cellulitis
- Pleural Effusions



# COMPLICATIONS FROM INTRAVASCULAR DEPLETION

- Prerenal azotemia
- Acute tubular necrosis
- Thrombosis

# WHEN TO GIVE ALBUMIN AND LASIX

- Peritonitis
- Pleural effusions
- Severe edema with skin breakdown/cellulitis

# WHEN NOT TO GIVE ALUMIN AND LASIX

- AESTHETIC PURPOSES

# HOW TO GIVE ALBUMIN AND LASIX

- 25% Albumin 1 gm/kg over 4 hours
- Lasix at hour #2 and upon completion
- Watch for hypertension and pulmonary edema

# STOP THE PROTEINURIA

- Prednisone 2 mg/kg/day (Max 80 mg/d)
- 80% WILL RESPOND WITHIN 2 WEEKS
- Best predictor of MCNS

# GOOD NEWS AND BAD NEWS

- MCNS will likely get better with steroids
- It will come back again and again and again
  - Especially a risk with intercurrent illness

# STRATEGIES TO PREVENT RELAPSES

- Prolong initial Prednisone therapy of 2 mg/kg/day for 6 weeks
- Taper off Prednisone over a 6 week interval

# SOME DEFINITIONS

- Frequent relapses
  - 4 or more relapses within a year
- Steroid dependence
  - 2 relapses consecutively on steroids or shortly after stopping
- Steroid resistance
  - No response to steroids after 4 weeks



THE MORE RELAPSES THE  
MORE STEROIDS

# SOMETIMES STEROIDS AREN'T SO GREAT

- Side effects of chronic steroid therapy:
  - Obesity
  - Poor growth
  - Osteoporosis
  - Cataracts
  - Striae
  - Diabetes

# WHEN GOOD STEROIDS GO BAD

- When excessive steroids are required to control nephrosis, consider a steroid sparing agent.
- Don't need to wait for development of steroid side effects.

# STEROID SPARING AGENTS

- Cyclophosphamide
- Mycophenylate
- Calcineurin inhibitors
  - Cyclosporine
  - Tacrolimus

# CHOICE OF STEROID SPARING AGENT

Depends on specific tissue diagnosis

# INDICATIONS FOR A RENAL BIOPSY

- Steroid resistance
- Need for a steroid sparing agent
- Adolescent
- Infant

# MINIMAL CHANGE DISEASE

- Steroid sparing agent of choice:
  - Cyclophosphamide
    - 3 mg/kg/day over 8 weeks
    - Monitor carefully for side effects

# SIDE EFFECTS OF CYTOXAN

- Hemorrhagic Cystitis
  - Encourage good intake of fluids
  - Monitor urine specific gravity
- Neutropenia
  - Frequent blood draws to follow ANC
- Infertility
- Hair loss
- Infections



# ADVANTAGES OF CYTOXAN

- Can anticipate a prolonged (one year or more) medication free remission

# TAKE HOME MESSAGE

- Taking care of patients with Nephrotic Syndrome is interesting and rewarding
- It is not too late to do a nephrology fellowship