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
NONORTHOSTATIC
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
- Cr=0.5
- Na=131
- K=3.8
- Cl=115
- Bicarb=24
- Alb=1.5
- Chol=360
- Trig=300
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 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