Hematuria, Proteinuria and the Changing Face of Glomerulonephritis

Pediatric Board Review
August 28, 2012
Robert J. Cunningham III, M.D.

Objectives

• Following this session the participant should be able to:
   Name the three most common causes of both nephrotic syndrome and of hematuria seen in the pediatric population
   List three indications for renal biopsy in proteinuric patients
   List three causes of nephritis associated with a depressed C3 level

Proteinuria

• The most severe form of proteinuria results in the nephrotic syndrome; therefore, the first part of this discussion will focus on the diagnosis, treatment, and prognosis of nephrotic syndrome. Then, I will outline an approach to children with less severe forms of proteinuria.
International Study of Kidney Disease in Children

- All nephrotics > 1 year and < 17 yrs of age were biopsied.
  - Minimal Change disease 76%
  - Focal Segmental Sclerosis 8.6%
  - Membranoproliferative GN 7.5%
- The first report was based on 521 biopsies and the final report on > 700 renal biopsies

Nephrotic Syndrome: Clinical Characteristics at Dx

- Characteristics
  - Age < 6 years
  - % Female
  - Hypertension (> 98%)
  - Hematuria
  - Low C1
  - Cholesterol ≤ 250mg/dL
  - Increased Creatinine
  - Response to prednisone
- Minimal Change
  - 79.6%
  - 39.9%
  - 13.5%
  - 23%
  - 1.5%
  - 5.4%
  - 32.5%
  - 93%
Nephrotic Syndrome: Clinical Characteristics at Dx

**Characteristics**
- Age < 6 years
- % Female
- Hypertension (>98%)
- Hematuria
- Low C₃
- Cholesterol <250mg/dL
- Increased Creatinine
- Response to prednisone

**Focal Segmental**
- 50%
- 30.6%
- 33.3%
- 48%
- 3.7%
- 8.6%
- 40.6%
- 7%
Focal Segmental Sclerosis is increasing in incidence

- In a study by Bonilla-Felix et al from Houston, comparing renal biopsy diagnoses prior to 1990 and from 1990-98, they found:
  - Biopsy prior to 1990: 23% FSGS
  - Biopsy after 1990: 47% FSGS
- The incidence of FSGS in patients > 8 yrs of age doubled from 33% to 67%
- Particularly pronounced in African American patients

Increasing Incidence of FSGS

- Study from the Children’s Hospital of Eastern Canada in Ottawa by Filler et al
  - Study covered 1985-2002
  - Population with mandatory referral to this center and covered 275,000 children.
  - The incidence of FSGS from 1985—94 was 0.37/100,000
  - From 1994 thru 2002, it was 0.97/100,000
Increasing Incidence of FSGS

- This is also true in young adults- ages 15-50 yrs of age. In the U.S., a survey of renal biopsies done from 1995-97 showed that 35% of biopsies showed FSGS.
- 50% of biopsies done in the black population showed FSGS
- Particularly susceptible are black males in adolescence or early adult (e.g. Athletes)

FSGS Therapy

- Most patients do not respond to steroids
- Cyclosporine Rx has been reported to decrease of eliminate proteinuria in up to 1/3 of patients
- Newer therapies include Tacrolimus, Mycophenolate, Rapamycin
- This disease may recur in 30% of Transplants !! And we cannot predict which ones.

FSGS Therapy

- Non specific therapies include ACE inhibitors and Angiotensin Receptor Blockers.
- These agents make sense if there is a reduction in renal mass and the genesis of the lesion appears to be “hyperfiltration nephropathy”
Factors that affect renal perfusion and filtration

Renal Autoregulation

- Prostacycline
- Angiotensin I
- Angiotensin II
- Renin
- PGE₂

Nephrotic Syndrome: Clinical Characteristics at Dx

- Characteristics
  - Age < 6 years
  - % Female
  - Hypertension (>98%)
  - Hematuria
  - Low C₁
  - Cholesterol ≤250mg/dL
  - Increased Creatinine
  - Response to prednisone

- MPGN
  - 2.6%
  - 64.1%
  - 27%
  - 48%
  - 74%
  - 19.4%
  - 50%
  - 0

Nephrotic Syndrome: Clinical Characteristics

- Patients with Minimal Change Disease respond to prednisone and there is no evidence that patients with Focal Segmental Glomerulosclerosis are harmed in any way by prednisone treatment.
- Patients with Membranoproliferative GN may develop severe hypertension when treated with daily prednisone.
Nephrotic Syndrome: Clinical Characteristics

* Therefore, patients who are suspected of having minimal change or FSGS are treated with prednisone, and a renal biopsy is performed only if they fail to respond.
* If a patient is thought to have MPGN, a renal biopsy is performed prior to any treatment.

Minimal Change Nephrotic Syndrome: Complications

* Peritonitis
  * Most common organism is *Strep. Pneumonia*
  * *E. Coli* is the next most common offender
  * Aseptic peritonitis next most commonly seen
* Thrombosis and pulmonary embolism
* Mortality remains 5%

Response of Patients with Minimal Change Disease to Prednisone

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responder</td>
<td>93%</td>
</tr>
<tr>
<td>Non responder</td>
<td>7%</td>
</tr>
<tr>
<td>Minimal Change</td>
<td>100%</td>
</tr>
</tbody>
</table>
Response of Patients with Minimal Change Disease to Prednisone

- Prednisone Responder: 93%
- Non Relaper: 36%
- Infrequent Relaper: 18%
- Frequent Relaper: 39%
- Subsequent Non-responder: 5%

Minimal Change Disease: Frequent Relapses

- Patients who relapse frequently are more subject to the complications of both the disease and to the side effects of prednisone Rx.
- Therefore, alternate therapies are employed, and they include cyclophosphamide, chlorambucil, and cyclosporine, tacrolimus.

Nephrotic Syndrome

- Response to prednisone therapy is usually within 8 weeks. If patients do not respond in this time frame, there is no utility in continuing. This exposes the patient to both the ill effects of the disease and side effects of the treatment.
Nephrotic Syndrome < 1yr

- Congenital Nephrotic Syndrome
  - Presents early in life
  - Massive anasarca
  - History of a large placenta
  - May be an autosomal recessive (Finnish type)
  - Death by 1 year of life (E.Coli sepsis)
  - Treatment is daily albumin infusions, nephrectomy, dialysis, and transplant

What about proteinuria?

- Orthostatic Proteinuria is seen in teenagers
- Described in WW II
- Group of GI’s who only spilled protein when they were standing; when in the supine position, no protein in urine
- 40 yr follow up shows no increase in renal disease or hypertension in these GI’s
An Approach to Proteinuria

- As shown in the attached table, the approach to the patient with less severe forms of proteinuria is age dependent and relies on the information about the nephrotic syndrome.
- Patients < 7 years of age are approached as though they have minimal change disease.

Patients > 7 years of age are more likely to be renal biopsy candidates because the probability is much greater that they will have a histologic lesion other than minimal change.
Hematuria

• Hematuria is much less worrisome to the nephrologist than is proteinuria. The evaluation of a patient with both hematuria and proteinuria would follow the guidelines already presented for the evaluation of proteinuria.
• The most important step in the evaluation of a patient with hematuria is to determine if this is an isolated finding.

Hematuria

• The presence of concomitant hypertension, edema, and/or abnormal renal function should make Glomerulonephritis a consideration.
  • Then you must obtain a history looking for strep exposure, consider obtaining strep titers and a C3.

Hematuria

• The algorithm for evaluation of isolated hematuria is appended
• The primary considerations are
  • Hypercalciuria
  • IgA nephropathy
  • Sickle Cell trait
  • UTI
  • Hydronephrosis
Hematuria

* Hypercalciuria
  - 70% of patients with increased urinary calcium excretion have a + family history for renal stones
  - Patients may complain of dysuria and/or frequency
  - Ca/Cr on a random urine is > 0.2 and a 24 hour urine for Ca is > 4mg/kg/24 hours
Hematuria

- Hypercalciuria
  - Treatment is to increase fluid intake, reduce the Na intake, increase the dietary K.
  - A thiazide diuretic may also be used which decreases the urinary excretion of calcium.
  - DO NOT decrease dietary calcium intake!

- IgA Nephropathy
  - This is a diagnosis that can be made definitively only by renal biopsy.
  - Clinically, these patients may have persistent microscopic hematuria. Repeated episodes of gross hematuria with minor infections is very characteristic.
  - 85% of these patients do well.
Hematuria

- IgA Nephropathy
  - The 10-15% of patients who develop chronic disease and are at risk for renal failure have or develop proteinuria.
  - The appearance of persistent proteinuria is a reason to perform a renal biopsy.

Hematuria

- Sickle Cell Trait
  - Hematuria is more commonly seen with trait than with disease.
  - Patients may develop severe hematuria, and this can be very difficult to treat. It is rarely a serious problem in the pediatric population.

Hematuria

- Other causes of hematuria include UTI, Alport’s syndrome (so a family history of renal disease is very important), and hydronephrosis.
- Patients who develop gross hematuria with minor trauma should have renal imaging studies to look for hydronephrosis.
Hematuria

- Cancer is a concern of parents, and this must be addressed. Hematuria is not a presenting sign for most pediatric tumors. Wilms tumor may have hematuria, but the mass is usually evident on exam. The only other case of hematuria as the presenting sign of cancer, that I have seen, was a patient with a renal sarcoma, which is a very rare lesion.

Laboratory Studies for Patient with isolated Hematuria

- U/A
- Serum electrolytes, creatinine, BUN
- CBC
- Urine Calcium/Creatinine ratio
- Sickle Cell screen in at risk patients
- Renal ultrasound – with gross hematuria
- Urine culture if symptoms or evidence of pyuria

Hematuria: Glomerular causes

- Secondary to Systemic Diseases
  - SLE - will have low C₃
  - HSP
  - HUS
  - SBE - will have low C₃
  - Shunt Nephritis-ventricular atrial shunt
    • will have low C₃

- Primary Renal Disease
  - Post Strep GN - will have low C₃
  - Membranoproliferative GN - will have low C₃
  - IgA Nephropathy - hematuria increased with viral infections
  - Thin basement membrane disease (familial)
Hematuria: Nonglomerular Causes

- Kidney Stones
- Hypercalcuria
- Hemoglobinopathies
  - SS disease, Sickle cell trait, SC disease
- Vascular Malformations
- Thrombocytopenia
- Polycystic kidneys
- Tuberous Sclerosis with angiomyolipomas
- Tumors (rare & can usually palpate the tumor)
- Obstruction

Questions

1. A four year old boy who presented with swelling, ascites and a cholesterol of 648 mg/dl one month ago presents today for a re-evaluation following a one-month course of prednisone (2 mg/kg/day) and furosemide (40 mg/day). Today he has less swelling, but still has 4+ proteinuria. What is the most likely diagnosis?
   A) Minimal change nephrotic syndrome
   B) Focal segmental sclerosis
   C) Membranoproliferative glomerulonephritis
   D) Post-streptococcal glomerulonephritis
   E) IgA nephropathy

Questions cont.

2. A four year old boy who presented with swelling, ascites and a cholesterol of 648 mg/dl one month ago presents today for a re-evaluation following a one month course of prednisone (2 mg/kg/day). His proteinuria has cleared, but every time his prednisone dose is switched to qod, his proteinuria returns. What is the most likely diagnosis?
   A) Minimal change nephrotic syndrome
   B) Focal segmental sclerosis
   C) Membranoproliferative glomerulonephritis
   D) Post-streptococcal glomerulonephritis
   E) IgA nephropathy
3. A seven year old girl has crampy abdominal pain and a rash on the back of her legs and buttocks as well as on the extensor surfaces of her forearms. Laboratory analysis reveals proteinuria and microhematuria. She is most likely to be affected by which of the following?
A) Systemic lupus erythematosus
B) Anaphylactoid purpura
C) Poststreptococcal glomerulonephritis
D) Polyarteritis nodosa
E) Dermatomyositis

4. A ten year old boy presents with a history of hematuria for the past eight months and 1+ proteinuria. The hematuria is more pronounced when he has a URI. He will likely show which one of the following signs?
A) A low C3 complement
B) A urinalysis with calcium oxalate crystals
C) A urine with an S.G. = 1.020, pH = 5.0 and an RBC cast on microscopic exam
D) Evidence of hemolytic anemia with a smear demonstrating anisocytosis and poikilocytosis with very few platelets

5. The finding one might expect in a six year old boy with brown urine and healing impetigo include each of the following except:
A) Hypertension
B) Dyspnea
C) Periorbital edema
D) Hepatomegaly
E) Polyuria
Answer Key

- Case 1: B
- Case 2: A
- Case 3: B
- Case 4: C
- Case 5: E