

Seventeen year old female with ADHD.
Vomited every night for one year. No weight loss, hematemesis, hematochezia etc.
Then, sore knees on stairs, then elbows and ankles.
Noted to have normochromic anemia, and elevated sedimentation rate and C reactive protein.
Urine contains red blood cells and protein.

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ADOLESCENT
MEDICINE
CLINICS

1-1

Glomerulonephritis



Keith K. Lau, MD^{a,b}, Robert J. Wyatt, MD, MS^{a,b,*}

^a*Division of Pediatric Nephrology, Department of Pediatrics,
University of Tennessee Health Sciences Center, Room 301, WPT, 50 North Dunlap,
Memphis, TN 38103, USA*

^b*Children's Foundation Research Center at the Le Bonheur Children's Medical Center, Room 301,
WPT, 50 North Dunlap, Memphis, TN 38103, USA*

Early diagnosis of glomerulonephritis (GN) in the adolescent is important in initiating appropriate treatment and controlling chronic glomerular injury that may eventually lead to end-stage renal disease (ESRD). The spectrum of GN in adolescents is more similar to that seen in young and middle-aged adults than to that observed in prepubertal children. In this article, the authors discuss the clinical features associated with GN and the diagnostic evaluation required to determine the specific type of GN. **With the exception of hereditary nephritis (Alport's disease), virtually all types of GN are immunologically mediated with glomerular deposition of immunoglobulins and complement proteins. The inflammatory events leading to GN may be triggered by a number of factors. Most commonly, immune complexes deposit in the glomeruli or are formed in situ with the antigen as a structural component of the glomerulus. The immune complexes then initiate the production of proinflammatory mediators, such as complement proteins and cytokines. Subsequently, the processes of sclerosis within the glomeruli and fibrosis in the tubulointerstitial cells lead to chronic or even irreversible renal injury [1].** Less commonly, these processes occur without involvement of immune complexes—so-called “pauci-immune GN.”

* Corresponding author. Room 301, WPT, Children's Foundation Research Center, 50 North Dunlap, Memphis, TN 38103.

E-mail address: rwyatt@utm.edu (R.J. Wyatt).

Presentation and diagnostic evaluation

2

The hallmark of GN is inflammation within the glomeruli that typically manifests as hematuria and proteinuria (Box 1). Renal function may be normal or reduced, depending on the severity of the acute condition or the presence of chronic glomerular injury. Patients often have a normal physical examination and blood pressure. However, sometimes they may present with any combination of oliguria, hypertension, and edema. Some types of GN have other associated findings, such as a vasculitic rash, arthritis, or even pulmonary hemorrhage.

2-1

The hematuria can be macroscopic (visible) or microscopic. Microscopic examination of the urinary sediment characteristically shows dysmorphic red blood cells (RBCs) and often RBC casts. Dysmorphic RBCs can be detected with routine microscopy but are best detected by phase contrast microscopy. Greater than 30% of RBCs exhibiting dysmorphic features, such as doughnut shape and blebs, is a highly sensitive indicator of glomerular disease [2,3]. The degree of proteinuria may vary from normal (<4 mg/m²/h) to nephrotic range (>40 mg/m²/h). A random urine protein-to-creatinine ratio provides information as acceptable as that of a timed (usually 24-hour) collection, with normal being less than 0.2 and nephrotic range being greater than 2.0.

Except in the typical case of poststreptococcal acute glomerulonephritis (PSAGN) with normal or transiently decreased renal function, renal biopsy is required to determine the precise diagnosis and severity of the glomerular involvement. Either consultation or referral to a nephrologist is necessary when the primary care physician suspects GN other than mild or typical cases of PSAGN. Certain blood tests will provide clues to the diagnosis and, in some instances, become markers for response to treatment. Baseline blood tests include complete blood count, creatinine, complement (C3 and C4), and streptococcal serology (antistreptolysin O and Streptozyme). Among all types of GN (Box 2), the ones associated with significant depression of serum C3 concentration are PSAGN, membranoproliferative glomerulonephritis (MPGN), systemic lupus erythematosus (SLE), nephritis of chronic bacteremia (ventriculo-atrial shunt and

3

Box 1. Presenting signs and symptoms of glomerulonephritis

- Hematuria**
 - Macroscopic (visible) or microscopic
 - Dysmorphic RBCs and RBC casts
- Proteinuria**
- Hypertension**
- Edema**
- Renal insufficiency**
 - Transient
 - Progressive

Box 2. Differential diagnosis of glomerulonephritis*Poststreptococcal acute glomerulonephritis**IgA nephropathies*

IgA nephropathy (Berger's disease)

Henoch-Schönlein

Membranoproliferative glomerulonephritis

Idiopathic—types I, II, III

Secondary—nephritis of chronic bacteremia, hepatitis B and C, alpha-1 antitrypsin deficiency, etc.

*C1q nephropathy**Membranous nephropathy—typically presents with nephrotic syndrome**Alport syndrome**Antiglomerular basement membrane disease**Antineutrophil cytoplasmic autoantibody (ANCA) glomerulonephritis**Pauci-immune ANCA-negative glomerulonephritis**Systemic lupus erythematosus*

subacute bacterial endocarditis), and hepatitis B GN. Significant C4 activation manifested by depression of serum C4 concentration is typically seen in SLE and sometimes in type I MPGN. The presence of systemic manifestations warrants a more extensive battery of diagnostic tests based on the diseases in the differential diagnosis (discussed later in this article for each specific disease).

3-1

Principles of therapy

Current treatment of GN has two main objectives: control of inflammation and inhibition of fibrosis. Anti-inflammatory agents include intravenous or oral corticosteroids, cyclophosphamide, azathioprine, mycophenolate mofetil, and fish-oil supplements containing omega-3 fatty acids. Drugs that reduce proteinuria will inhibit tubular injury and fibrosis [1]. These may include angiotensin-converting enzyme inhibitors (ACEi), angiotensin 2 receptor blockers (ARB), and perhaps statins and anti-oxidants. Specific treatments will be discussed in each section.

4

3-1

Acute glomerulonephritis

An adolescent with GN may present with signs and symptoms that require immediate intervention. One scenario is a presentation of renal insufficiency that

worsens daily, as evidence accumulates that the patient does not have PSAGN. Such patients may have rapidly progressive GN (RPGN) that is characterized pathologically by crescents forming from the cells of Bowman's capsule. If the process progresses, the crescent will irreversibly destroy the glomerular tuft. ESRD may occur within weeks of the onset of this process. This process is a true emergency that requires prompt referral to a nephrologist. Treatment with high-dose intravenous methylprednisolone and, in some cases, plasmapheresis may halt the process [4–7]. Another scenario is the occurrence of hypertensive encephalopathy or pulmonary edema at the onset of PSAGN. Adolescents who present with hypertension should be admitted to control the blood pressure and prevent these complications.

Rapidly progressive glomerulonephritis

RPGN may be diagnosed in the adolescent who presents with macroscopic hematuria and is found to have an elevated serum creatinine that continues to rise on a daily basis. Nonspecific symptoms such as fatigue and lethargy are common. Often the macroscopic hematuria persists until well after the initiation of treatment with intravenous methylprednisolone. Typically, more than 50% of the glomeruli should be affected with crescents for a case to be classified as RPGN [8]. All of the immunologically mediated types of GN may present as RPGN, but the types most frequently associated with it are antiglomerular basement membrane (anti-GBM) disease, antineutrophil cytoplasmic autoantibodies (ANCA) GN, and Henoch-Schönlein purpura nephritis (HSPN). PSAGN may also have crescent formation and in some cases will fit the definition of RPGN. The rarity of RPGN in children and adolescents is illustrated by a pediatric series that found crescents in 56 of 372 biopsy specimens, with only two meeting criteria for classification as RPGN [9]. Often pediatric nephrologists will treat patients with fewer than 50% of glomeruli affected with crescents as if they had RPGN. Despite aggressive therapy, the outcome is often progression to ESRD. Early diagnosis and aggressive treatment are the most important factors in preservation of renal function.

Poststreptococcal acute glomerulonephritis

Early descriptions of PSAGN were based on the description of epidemics or clusters of cases usually related to pyoderma, with many cases being asymptomatic [10–12]. The peak age at occurrence was 4 to 5 years; few cases were diagnosed in adolescents. In the latest pediatric series from Memphis, only 11% were age 13 or older (S. Roy, personal communication, 2004). At the present time, cases tend to occur more sporadically, with more due to pharyngitis than to pyoderma, and the incidence in both the United States and other countries is declining [13–15].

The diagnosis of PSAGN is based on clinical features, depression of serum C3 concentrations, and the presence of streptococcal antibodies or enzymes in-

that trigger the nephritogenic response and activate the alternative complement pathway are most likely related to specific nephritogenic M proteins [24].

With the rare exception of severe crescentic PSAGN, which potentially may progress to ESRD, the outcome of PSAGN is excellent. The clinical signs usually resolve within several weeks, followed by cessation of proteinuria and hematuria. Microscopic hematuria may persist for several months, but the urinalysis is usually normal by 6 to 12 months. The occurrence of a second new case of PSAGN in the same child is well documented [25].

Chronic or persistent glomerulonephritis

Most types of GN will enter a chronic or persistent phase. Often such patients are at risk for continued glomerular injury that potentially could result in ESRD. Commonly, patients with GN that began in childhood or adolescence do not reach ESRD until adulthood. Progression to ESRD in adolescents with chronic GN may be delayed or even avoided with attention to the principles of renal protection [26]. This attention involves aggressive control of hypertension and treatment of proteinuria for both normotensive and hypertensive patients with an ACEi or an ARB. These agents are effective in reducing proteinuria in virtually all forms of chronic GN. Many adolescents and young adults exhibit poor compliance with regard to taking their medications. The primary care physician plays an important role in monitoring control of hypertension, encouraging compliance with medications, and stressing the importance of regular follow-up by the nephrologist. In addition, the physician should be aware of ACEi fetopathy as a major risk for pregnant adolescents so that the drug may be stopped immediately if the patient becomes pregnant. ACEi and ARB therapy should be used cautiously in adolescents at risk for dehydration, particularly in the football player involved in summer practice who has an increased risk for development of prerenal azotemia.

5

IgA nephropathy

IgA nephropathy (IgAN) is the most commonly diagnosed type of glomerulonephritis in the adolescent. Sixty-two percent of 47 patients at the authors' institution were age 13 or older at the time of biopsy [27]. In 1969 Jean Berger [28] reported the finding of deposition of IgA in the mesangium of the glomerulus in children and adults who experienced an episode of macroscopic hematuria during an episode of pharyngitis. This classic presentation of macroscopic hematuria at the time of a respiratory infection is the event that usually results in the referral of the adolescent to a nephrologist who performs the biopsy necessary for diagnosis. At the authors' institution, they recommend a biopsy when the urine protein-creatinine ratio is more than 0.5. They sometimes

should be aware of the potential complications of these immunosuppressive agents, such as bone marrow depression and opportunistic infections.

Summary

GN in the adolescent requires prompt diagnosis. When even mild degrees of renal insufficiency are documented, immediate referral to a nephrologist is necessary to ensure that serious conditions, such as RPGN, are correctly diagnosed and aggressively managed. In an adolescent with macroscopic hematuria, the demonstration of dysmorphic RBCs, RBC casts, and proteinuria indicates that the bleeding is of glomerular origin. Physicians caring for adolescents with chronic GN should have a basic understanding of the specific disorders. They may be involved in blood pressure monitoring and should be aware of the potential side effects of the antihypertensive and immunosuppressive medications used in patients with GN.

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2-1

Dec 11, 2011 7:01 PM, Mann WS

Microscopic exam of sediment characteristically shows dysmorphic red cells on routine microscopy but best on phase contrast.

Greater than 30% is highly sensitive for glomerular disease.

Random protein to creatinine ratio is acceptable, compared to 24 hour collection, with normal being less than 0.2 and greater than 2.0 indicating nephrotic range.

3-1

Dec 11, 2011 6:34 PM, Mann WS

An adolescent may present with daily worsening renal failure. Non-specific symptoms such as fatigue and lethargy are common.

This is a true emergency and may require intravenous methylprednisolone in high doses and nephrology consult.

This constitutes RPGN. (Rapidly Progressive Glomerulonephritis)

If proteinuria is in nephrotic range and edema is present, diurese with Lasix.

If RPGN suspected, avoid ACE inhibition unless concern has passed. Treat elevated blood pressure with beta blockade.

1-1

Dec 11, 2011 9:52 PM

1. What is wrong with her?
2. Is this glomerulonephritis?
3. Why?
4. Can you diagnose this from urinalysis?
5. How do you measure proteinuria?
6. How urgent is this?
7. What is RPGN?
8. Does she require renal biopsy?
9. What is the initial treatment?
10. What is significance of low C4 complement?

3-1

Dec 11, 2011 9:58 PM, Mann WS

If there is edema secondary to proteinuria, treat with Lasix.

If there is concern about the possibility of rapidly progressive glomerulonephritis, postpone the use of ACE inhibition and treat elevated blood pressure with beta blockade.