Glomerulonephritis in Children — Signs and Symptoms

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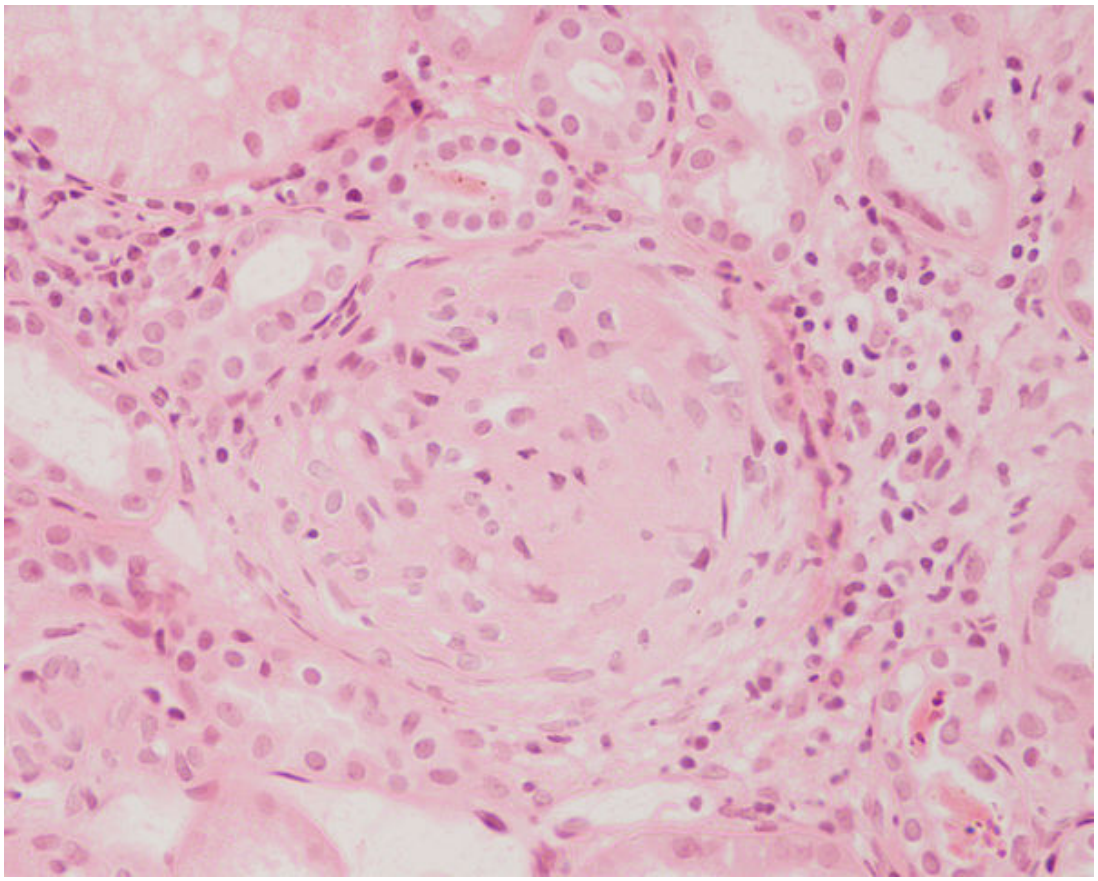
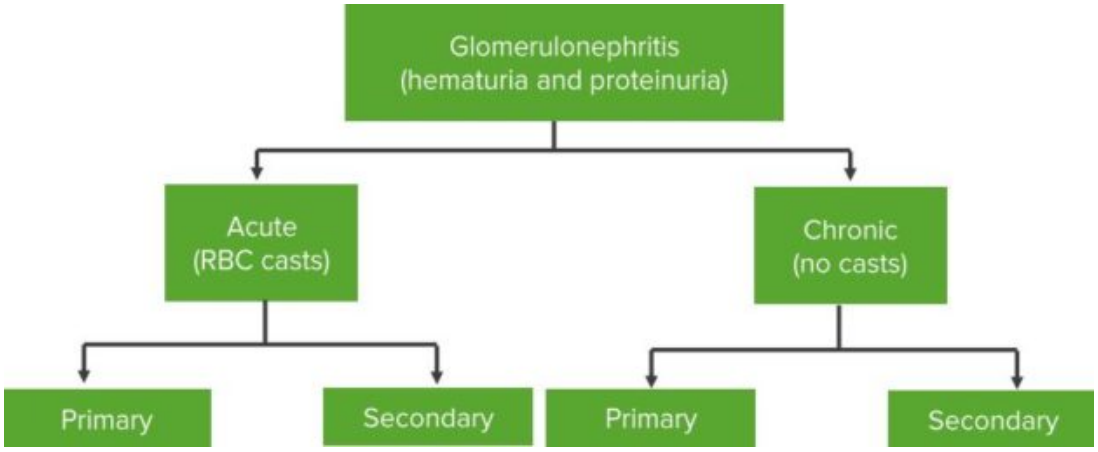
Glomerulonephritis (GN) represents a range of disorders of the glomeruli that are immune-mediated. A common histopathological finding is the presence of immune complexes trapped and deposited in the glomeruli. GN usually presents with hypertension, hematuria, proteinuria, and/or renal function deterioration, and complications thereof.



Definition of Glomerulonephritis in Children

Acute GN is **defined as glomerular injury that is accompanied by inflammation of the glomeruli.** It is a clinical constellation of sudden onset of hematuria and proteinuria, edema, hypertension with or without RBC casts. Pediatric chronic GN includes both primary GN (e.g. IgA nephropathy) and secondary GN (e.g. Systemic lupus erythematosus nephritis).



"Glomerulonephritis Pathology" Image created by Lecturio

Epidemiology and Etiology of Glomerulonephritis in Children

GN occurs when immune complexes are trapped in the renal parenchyma. **Pediatric GN can be classified based on clinical presentation into four types:**

- Acute GN
- Rapidly progressive GN
- Recurrent macroscopic hematuria
- Chronic GN

Acute (RBC casts)		**Chronic (no casts)**	
Primary	**Secondary**	**Primary**	**Secondary**
• PSGN • Infectious GN • IgA Nephropathy (Berger´s disease) • MPGN	• HSP • SLE • Polyarteritis Nodosa • Hemolytic uremic syndrome (HUS) • Subacute endocarditis • Goodpasture syndrome	• MPGN • Membranous nephropathy • Focal glomerulosclerosis • Mesangial proliferative nephritis	Same as acute secondary causes: • HSP • SLE • Polyarteritis Nodosa • Hemolytic uremic syndrome (HUS) • Subacute endocarditis • Goodpasture syndrome

Classification of Glomerulonephritis in Children

It can also be classified based on etiology.

Primary glomerulonephritis which includes:

- Acute post-streptococcal GN usually occurs in children older than age of 2 years. The **incidence is about 4 times higher in developing countries than in developed countries**.
- IgA nephropathy usually does not occur before adolescence (mostly males). It is the most common cause of acute glomerulonephritis in children.
- Membranoproliferative GN (MPGN) which occurs in children older than 8 years.

Secondary glomerulonephritis which arises from:

- Henoch–Schönlein purpura occurs in children aged 8 years or older. **Henoch–Schönlein purpura is the most common cause of secondary glomerulonephritis**.
- Granulomatosis with polyangiitis
- Microscopic polyangiitis
- Systemic lupus erythematosus

Acute post-streptococcal GN usually occurs in children older than age of 2 years. The **incidence is about 4 times higher in developing countries than in developed countries**. IgA nephropathy usually does not occur before adolescence (mostly males). It is the most common cause of acute glomerulonephritis in children.

Similarly, membranoproliferative GN (MPGN) and Henoch–Schönlein purpura occur in children aged 8 years or older. **Henoch–Schönlein purpura is the most common cause of secondary glomerulonephritis**. There seem to be no racial differences.

Pathophysiology of Glomerulonephritis in Children

The pathogenesis of GN remains somewhat unclear, despite advances in medicine. The pathophysiology involves an immune response due to infections or some non-infectious conditions which, in turn, activates a number of biological processes (complement activation, leukocyte recruitment, cytokine release, etc.) that lead to glomerular injury and increase the permeability of the glomerular basement membrane.

The circulating immune complexes (antigen-antibody complexes or other mechanisms) get trapped in the renal tissue and deposited in the glomerular basement membrane. Inflammation and proliferation of endothelial, mesangial, epithelial cells ensue, which damages normal renal tissue.

The inflammatory process can be self-fueling and can result in continued additional injury. For instance, cytokine release leads to phagocyte recruitment and formation of a membrane attack complex (MAC), which causes further damage. If the inflammatory process is stopped, as occurs in acute post-streptococcal GN, renal tissue recovers. Otherwise, there is a progressive loss of glomeruli and nephrons (e.g. membranoproliferative GN).

Acute Poststreptococcal GN: here, the etiological agent is obvious – streptococci, especially the group A beta-hemolytic streptococci. However, it has been proposed that there are nephritogenic strains of group A beta-hemolytic streptococci, which differ from rheumatogenic strains.

This would explain the difference in responses to the immune complexes that lead to two different diseases (post-streptococcal GN and rheumatic fever, respectively). M proteins, M-like proteins, and other factors on streptococci have been identified as the trigger for initiating a more nephritogenic process. Antigenic mimicry between proteins in the pathogen and those in the heart and kidneys lead to the formation of the immune complexes as the body mounts an immune response against its own proteins.

Clinical Features of Glomerulonephritis in Children

The **most frequent symptom is the change of urine color, which is usually due to hematuria.** The urine is typically reddish-brown (‘tea’ or ‘cola’ colored) in color. This is called gross hematuria. (When blood is present in urine, but does not affect the color and is found in urine microscopic analysis instead, it is called microscopic hematuria). If

the color is bright red, it signifies additional structural problems, such as stone formation.

The urination is often painless. **Pain during urination with gross hematuria should arouse suspicion of acute hemorrhagic cystitis**. Complications related to GN might cause symptoms and signs ranging from dyspnea to altered mental status.

Upon physical examination, various signs, such as high blood pressure (depending on the age and sex of the child), altered mental status, tachypnea, dyspnea, tachycardia, and cervical lymphadenopathy may be found. Abdominal examination may reveal ascites (nephrotic disease), hepatomegaly or splenomegaly, abdominal pain, scrotal edema, and so on.

Fluid retention may lead to some peripheral edema, but it may not be pitting. **In acute GN, the skin may show the characteristic rash of HSP, which may initially not be overt**. It may be restricted to feet or buttocks. Joint involvement occurs in some multisystem disorders with acute GN.

Glomerulonephritis is manifested in the following spectrum of symptoms:

- Hematuria (macroscopic or microscopic)
- Dysmorphic RBCs and RBC casts in the urine
- Proteinuria that may reach nephrotic range (>3g in 24 hrs.)
- Hypertension
- Edema
- Renal insufficiency

The different clinical presentations include the following:

Acute GN: typical presentation includes the sudden onset of hematuria with or without proteinuria, decreased glomerular filtration rate, and salt-water retention. There is often edema and elevated blood pressure.

Rapidly progressive GN: acute, rapid, and progressive deterioration of renal function, sometimes even within days or weeks. Characterized morphologically by extensive crescent formation.

Recurrent macroscopic hematuria: IgA nephropathy, and sometimes Alport syndrome, present as transient episodes of macroscopic hematuria, usually occurring 1 – 2 days after an upper respiratory infection.

Chronic GN: in chronic GN, the signs, and symptoms may be few and not overt and urinalysis may reveal only microscopic hematuria or proteinuria.

In some cases, patients present at a later stage of disease with symptoms and signs of elevated blood pressure, renal function deterioration, proteinuria and/or hematuria. Renal biopsy shows only non-specific findings, such as glomerular sclerosis, fibrosis, and tubular atrophy.

Diagnosis of Glomerulonephritis in Children

Early diagnosis is important for starting proper treatment and halting the course of the disease, which may eventually lead to end-stage renal disease. The clinical presentation of the disease is important (e.g. GFR normal or reduced, presence or absence of systemic symptoms and family history, etc.) as it provides clues to the underlying cause.

Clinical Diagnosis

In addition to the presenting symptoms and signs mentioned above, a **history of previous episodes or (streptococcal) throat infection should be elicited to determine chronic GN** or post-streptococcal GN, respectively. It is also important to elicit family history, which may be positive in patients with SLE and membranoproliferative GN.

While taking the patient's history, the involvement of other systems (due to complications or from the point of view of differential diagnosis) must be ruled out. The **examination of the cardiopulmonary system should focus on assessing the effects of fluid overload**.

Laboratory Diagnosis

Urine: Hematuria (gross or microscopic), proteinuria (typically, 500 mg/d to 3 g/d), and RBC casts in the urine. Although the latter is diagnostic of glomerular bleeding, it is not usually found. Also, a 24-hour urine protein excretion rate or urine protein: creatinine ratio is needed to evaluate the renal function.

Serum: Serum complement levels. If abnormal, test for individual components (e.g. C3, C4). Low C3 and normal C4 is observed in post-strep glomerulonephritis. However, a low C3 and low C4 is observed in lupus, shunt nephritis, and bacterial endocarditis. The serum creatinine level is tested to monitor renal function.

Culture for throat and skin swabs may be positive in patients with an infectious etiology.

Imaging

Ultrasonography of the kidney should be performed to rule out other renal disorders, such as cysts and stones. It is also useful to determine the extent of fibrosis.

Histopathology of Glomerulonephritis in Children

A **renal biopsy is almost always required to establish a definitive diagnosis**. However, post-strep glomerulonephritis, hemolytic-uremic syndrome, and Henoch-Schönlein purpura does not require biopsy in patients.

Light microscopy: light microscopy is neither sensitive nor specific for GN. There is a lot of variation, as well as overlap, in findings, which precludes a definitive diagnosis. Nevertheless, light microscopy has clinical utility in correlating with the patient's clinical findings and prognosis. Light microscopic findings can be clubbed into diffuse proliferative GN (with lesions in most glomeruli) or focal GN (with lesions in less than 50% of the glomeruli).

Immunofluorescence microscopy: immunofluorescence microscopy may show deposits of IgG, IgA, IgM and complements in the glomeruli. The deposition pattern may be characteristic enough to allow identification of a specific disease.

Deposition Pattern	Condition
Granular deposits	Immune complex diseases
Linear deposition of IgG along the glomerular basement membrane	Anti-glomerular basement membrane antibody disease

Mesangial IgA > IgG	IgA nephropathy, Henoch–Schönlein purpura nephritis
No immunoglobulin deposit (indicating a pauci-immune response)	Systemic vasculitis

Electron microscopy: electron microscopy is useful for confirming a diagnosis because it reveals whether the deposits are in the mesangium or subendothelial/subepithelial tissues, or a combination thereof. Therefore, it can help establish a very specific diagnosis, e.g. minimal change disease, focal segmental glomerulosclerosis, thin basement membrane disease, etc.

Clinical Picture of Specific Diseases of Glomerulonephritis in Children

Acute Poststreptococcal GN: sudden-onset acute nephritis 1 – 2 weeks after a streptococcal throat infection and 3 – 6 weeks after a skin infection. However, a history of throat or skin infection may be absent. Detection of DNase B antigen is the best method of identifying a past streptococcal infection.

Acute post-streptococcal GN is one of the most common glomerular causes of gross hematuria in children and is an important cause of acute renal failure and hospitalization in children. Renal biopsy is not indicated if typical features are present. Specific renal biopsy changes include:

1. Lumpy bumpy deposits of immunoglobulin and complement on the glomerular basement membrane and the mesangium
2. Electron-dense deposits or ‘humps’ on the subepithelial side.

Serum C3 level may be acutely and markedly decreased, which is often diagnostic and return to normal at around 6 weeks of the disease.

Alport Syndrome: hereditary nephritis is usually an X-linked dominant disorder (although it can rarely be autosomal dominant or recessive). It can present as asymptomatic (microscopic) hematuria, and sometimes gross hematuria following a respiratory infection is seen.

Renal biopsy shows glomerular sclerosis, thick basement membrane, fibrosis, foam cells, and tubular atrophy. **There may be hearing loss and ocular abnormalities,** such as anterior lenticonus, which is pathognomic.

Differential Diagnoses of Glomerulonephritis in Children

- Anti-glomerular basement membrane antibody disease
- Antineutrophil cytoplasmic autoantibody (ANCA) GN
- C1q nephropathy
- IgA nephropathies
- (Idiopathic) Membranoproliferative GN (remains an important cause of glomerular disease in children)
- Pauci-immune ANCA-negative GN
- Systemic lupus erythematosus (antinuclear antibodies can help rule this out)
- Ureteropelvic junction obstruction
- Wilson disease

Treatment of Glomerulonephritis in Children

The **management of GN involves supportive care, as well as treatment of the underlying pathology.**

Supportive care

For GN, or indeed most renal diseases, supportive treatment involves the management of fluid-electrolyte balance and hypertension, as well as monitoring the renal function. **If there is fluid overload, diuretics, fluid restriction, and salt restriction are usually helpful**. Loop diuretics are helpful in fluid overload, along with hypertension, although other antihypertensives such as angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers may be additionally needed.

Electrolyte abnormalities include hypocalcemia and hyponatremia, and if mild, can be resolved by managing fluid overload. Sometimes, calcium supplementation may be required. **Heavy physical exercise should be avoided**. If the renal function is too poor, e.g. in the setting of acute renal failure, dialysis will be needed.

Treatment of the underlying pathology

The treatment should be aimed at controlling inflammation and the inhibition of fibrosis. The former can be achieved by administering anti-inflammatory or immunosuppressive agents, such as corticosteroids (oral or systemic), cyclophosphamide, azathioprine, and mycophenolate mofetil.

To inhibit fibrosis, **therapy is targeted to reduce proteinuria and tubular injury**. Drugs that help achieve this include angiotensin-converting enzyme inhibitors and angiotensin 2 receptor blockers.

Note: Any persisting streptococcal infection in patients with post-streptococcal GN must be managed with penicillin administration.

Acute post-streptococcal nephritis

Antibiotics should be given to prevent the spreading of, or treat any existing infection if present. **Salt restriction and loop diuretics are often first-line therapies against hypertension**, and specific antihypertensive drugs may be added if needed.

Alport syndrome

There is **no specific therapy, and the prognosis is not good**. Angiotensin-converting enzyme inhibitors can retard disease progression. This usually requires dialysis and renal transplantation as there is a propensity to end-stage renal disease.

Progression and Prognosis of Glomerulonephritis in Children

Overall, the **prognosis of children with GN is generally good** as almost all cases of epidemic post-infectious GN often progresses to a complete recovery. Patients with focal GN have a better prognosis than those with diffuse proliferative GN, who tend to have a more serious disease. However, some children may develop end-stage renal disease. The

mortality of acute glomerulonephritis ranges from 0-7%. The sporadic cases are associated with a higher rate of chronic disease and the development of end-stage renal disease.

Review Questions

The correct answers can be found below the references.

1. Renal biopsy of a 7-year-old boy with the complaint of hematuria reveals the following: lumpy-bumpy deposits on the glomerular basement membrane and subepithelial humps-like deposits. Which of the following pieces of information would help establish a definitive diagnosis?

A. Proteinuria
B. Decrease of serum C3 level
C. Positive family history
D. Anterior lenticonus
E. Edema

2. An 8-year-old boy presents with microscopic hematuria, proteinuria, and hearing loss. Assuming positive family history, which of the following conditions is the most likely cause?

A. Acute post-streptococcal GN
B. Chronic kidney disease
C. Alport syndrome
D. Wilson disease
E. Nephrotic syndrome

3. Which of the following is the most common cause of acute glomerulonephritis in children?

A. IgA nephropathy
B. Membranoproliferative GN (MPGN)
C. Henoch–Schönlein purpura
D. Alport syndrome

References

Kliegman RM, Stanton BF, St. Geme III JW, Schor NF, Behrman RE, Editors. Nelson Textbook of Pediatrics, 20th Edition. Elsevier Saunders; 2011: 2498-2507.

Lau, K. K., & Wyatt, R. J. (2005). Glomerulonephritis. Adolescent medicine clinics, 16(1), 67.

Welch, T. (2012). An Approach to the Child with Acute Glomerulonephritis.International Journal Of Pediatrics, 2012, 1-3.

Singh, G. R. (2009). Glomerulonephritis and managing the risks of chronic renal disease. Pediatric Clinics of North America, 56(6), 1363-1382.

Chadban, S. J.,& Atkins, R. C. (2005). Glomerulonephritis. The Lancet, 365(9473), 1797-1806.

Eison, T. M., Ault, B. H., Jones, D. P., Chesney, R. W., & Wyatt, R. J. (2011). Post-streptococcal acute glomerulonephritis in children: clinical features and pathogenesis.

Pediatric Nephrology, 26(2), 165-180.

Madaio, M. P.,& Harrington, J. T. (2001). The diagnosis of glomerular diseases: acute glomerulonephritis and the nephrotic syndrome. Archives of internal medicine, 161(1), 25-34.

Couser, W. G. (1999). Glomerulonephritis. The Lancet, 353(9163), 1509-1515.

Pediatric Nephritis via emedicine.medscape.com

Overview of the pathogenesis and causes of glomerulonephritis in children via uptodate.com

Poststreptococcal Glomerulonephritis via emedicine.medscape.com/

Correct answers: 1B; 2C; 3A

Notes