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Classification of glomerulonephritis

Glomerulonephritis is an infectious allergic renal disease with primary lesions of glomeruli. Boys suffer twice more often than girls.

**Etiology and Epidemiology.**
Acute poststreptococcal glomerulonephritis follows infection of the throat or skin by certain "nephritogenic" strains of group A β-hemolytic streptococci. The factors that allow only certain strains of streptococci to be nephritogenic remain unclear. Poststreptococcal glomerulonephritis commonly follows streptococcal pharyngitis during cold weather months and streptococcal skin infections or pyoderma during warm weather months. Although epidemics of nephritis have been described in association with both throat (serotype 12) and skin (serotype 49) infections, this disease is most commonly sporadic.

### Classification of glomerulonephritis

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<th>Form</th>
<th>Activity of renal process</th>
<th>Condition of renal functions</th>
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| 1. Acute glomerulonephritis  
   a) with nephritic syndrome  
   b) with nephrotic syndrome  
   c) with isolated urinary syndrome  
   d) with nephrotic syndrome, hematuria and hypertension | 1. Period of initial manifestations  
2. Period of comprehensive manifestations  
3. Period of reverse development  
4. Transition to chronic glomerulonephritis | 1. Without disorders of renal functions  
2. With disorders of renal functions  
3. Acute renal insufficiency |
Acute glomerulonephritis (GN) presents with hematuria, oliguria, hypertension and volume overload (edema), which are the findings of the classic "nephritic syndrome". Acute GN (AGN) is associated with inflammation and proliferation of the glomerular tuft. Most AGN is immunologically mediated. In acute poststreptococcal glomerulonephritis (APSGN), immune complexes form with streptococcal antigens, localize on the glomerular wall, activate the complement system, and initiate a proliferative and inflammatory response. AGN may be rapidly progressive (RPGN). Chronic GN (CGN) implies that permanent damage has occurred.

Acute poststreptococcal glomerulonephritis (APSGN) is the most common form of glomerulonephritis in children. APSGN can occur in all ages but is most frequent in males between 5 and 15 years. APSGN can occur after either an upper respiratory tract or skin infection due to GABHS. It is more common after an infection of the throat. CGN occurs more often in teenagers and adults. There are genetic predispositions for familial GN (Alport, X-linked) and autoimmune etiologies (e.g., SLE-lupus nephritis). Goodpasture's disease (anti-basement membrane autoantibodies) also presents with a classic nephritic syndrome in conjunction with hemoptysis, but this condition is rare.

Important questions to ask the patient/caregiver include history of macroscopic (gross) hematuria (tea or cola colored urine, or red colored urine), sore throat, impetigo, prior URI at least 1 week previously or skin sores (impetigo) in the preceding 3-4 weeks (suggestive of APSGN), URI in the preceding few days (suggestive of IgA nephropathy), reduced urine output, dyspnea, fatigue, lethargy, headache or seizures (hypertensive encephalopathy). Also, symptoms of a systemic disease such as fever, vasculitic rash (especially on the buttocks and legs posteriorly), arthralgia and weight loss may be present. On physical exam, pay particular attention to hypertension, pallor, signs of volume overload (edema, jugular venous distention, hepatomegaly, crackles in the lung bases), impetigo and rash. For PSGN, edema (specifically, facial edema involving the periorbital area) is the most frequent presenting symptom. Dark colored or bloody urine is frequently not noticed by patients because the abnormal color is only visible when the urine is collected in a cup. The abnormal color is not noticeable in a urine stream unless the urine color is very dark.

Many patients with APSGN with isolated urinary syndrome are asymptomatic and do not seek medical care. Mild hypertension is often asymptomatic. The classic dark urine is often not noticed. Screening urinalysis may often identify persistent microhematuria which eventually resolves months later. Many of these cases are felt to be resolving APSGN cases which never presented for medical attention during the acute nephritis phase.

Throat culture for GABHS will be positive in 15-20% of patients with APSGN. CBC is normal in AGN and with chronic renal insufficiency a normocytic normochromic or hypochromic microcytic anemia will usually be found. Serum chemistries will reflect the degree of renal failure (BUN, creatinine, potassium and phosphate are all elevated, while calcium is decreased), which is usually mild. The ASO titer will be positive in 60% of patients with APSGN. The complement C3 serum level will be low in APSGN and in other causes of GN described below. Urine microscopy shows RBC casts and createn RBCs in AGN. EKG, CXR and renal ultrasound are other tests that should be considered. RBC casts indicate the presence of acute nephritis. WBC casts can also be seen in APSGN, interstitial nephritis and pyelonephritis.

During convalescence from APSGN, complement C3 levels return to normal within 6-8 weeks. Persistently low C3 levels indicate an etiology other than APSGN. Gross hematuria will generally resolve within 1 to 2 weeks. Microscopic hematuria may persist for a year or more.

Nephrotic syndrome describes the collection of clinical and laboratory findings secondary to glomerular dysfunction, resulting in proteinuria. The diagnostic criteria are marked proteinuria, generalized edema, hypoalbuminemia, and hyperlipidemia (with hypercholesterolemia). The proteinuria in nephrotic syndrome is severe, exceeding 50 mg of excreted protein for every kilogram of body weight over 24 hours. Primary nephrotic syndrome refers to diseases limited to the kidney, whereas secondary nephrotic syndrome indicates systemic diseases that include kidney involvement (e.g., diabetic nephropathy).

In healthy children (less than 18 years of age), the annual incidence of nephrotic syndrome is 2-7 new cases per 100,000. The prevalence is approximately 16 cases per 100,000 children, making nephrotic syndrome one of the most frequent reasons for referral to a pediatric nephrologist. Also, the most common type of nephrotic syndrome is recurrent to some degree, so cases will often manifest repeatedly over time. The peak age for the onset of nephrotic syndrome is 2-3 years of age. In early...
The hallmark of nephrotic syndrome is severe proteinuria, most reliably diagnosed using a 24-hour urine collection. Spot urinalysis is also informative and reveals +3 to +4 proteinuria (300 to 1000 mg/dL), with a specific gravity usually greater than 1.020. Gross hematuria is not common. Blood samples show decreased albumin levels usually less than 2.0 mg/dL and elevated triglyceride and cholesterol levels.

Children with idiopathic nephrotic syndrome secondary to minimal change disease usually present with edema. Clinically apparent edema usually is not seen until albumin levels drop below 2 g/dL. The edema is initially noted around the eyes and in the lower extremities. Over the course of a day, the edema often generalizes and there can be weight gain.

The edema increases in permeability, resulting in pronounced proteinuria. The normal glomerular wall is remarkably selective for retaining protein in the serum. Once this selectivity is lost, the excretion of large amounts of protein will follow. This increase in permeability is related to the loss of negatively charged glycoproteins within the capillary wall that usually repel negatively charged proteins. The predominant protein lost is albumin, although immunoglobulins are also excreted. The pathophysiology of the formation of edema is incompletely understood. A simplification of the predominant theory is that after the plasma albumin concentration drops, secondary to protein excretion, the plasma oncotic pressure drops. With the decrease in oncotic pressure, fluid moves from the intravascular space to the interstitial space causing edema. The liver has a very large capacity to synthesize protein, so the persistent hypoalbuminemia is likely not due entirely to increased losses. Reduction of the intravascular volume results in activation of the renin-angiotensin-aldosterone system. Sodium and water are retained, which further increases the edema. There are likely other factors involved in the formation of edema, because some patients with nephrotic syndrome have normal or increased intravascular volume.

The hyperlipidemia in nephrotic syndrome is characterized by elevated triglycerides and cholesterol and is possibly secondary to two factors. The hypoproteinemia is thought to stimulate protein synthesis in the liver, including the overproduction of lipoproteins. Also lipid catabolism is decreased due to lower levels of lipoprotein lipase, the main enzyme involved in lipoprotein breakdown.

There are three morphological patterns of syndrome, with minimal change disease making up 80-85% of the cases. In this condition, the glomeruli appear normal or have a minimal increase in the mesangial cells or matrix. As well as being the most common form of primary nephrotic syndrome, minimal change disease also has the mildest clinical course. The rest of this chapter will focus on this disease entity after briefly describing the other forms of primary nephrotic syndrome as well as secondary nephrotic disease also has the mildest clinical course.

The clinical course is variable with only a small percentage of patients going into remission. Unfortunately, the recurrence rate of focal segmental glomerular sclerosis can be as high as 40% after renal transplant.

Membranoproliferative glomerulonephritis accounts for roughly 7% of primary idiopathic nephrotic syndrome. These patients often have hematuria, hypertension and mild azotemia. Another characteristic finding is persistently depressed C3 levels. The clinical course is variable with only a small percentage of patients going into remission.

Membranous glomerulopathy is rare in the pediatric age group, but becomes more common into adolescence and adulthood. It is often associated with infections, with hepatitis B being the most common. The clinical course is variable, but the overall prognosis is good, with spontaneous remission of proteinuria occurring in 50-60% of cases.

There are many different causes of secondary nephrotic syndrome in children. These include multisystemic diseases such as systemic lupus erythematosus and Henoch-Schönlein purpura, malignancies such as Hodgkin disease or leukemia, drug or toxin exposures such as mercury, gold, penicillamine or bee sting, and infectious etiologies such as Epstein-Barr virus, cytomegalovirus and tuberculosis.

Children with idiopathic nephrotic syndrome secondary to minimal change disease usually present with edema. Clinically apparent edema usually is not seen until albumin levels drop below 2 g/dL. The edema is initially noted around the eyes and in the lower extremities. Over the course of a day, the edema often generalizes and there can be weight gain. Patients or parents may notice tighter fit of clothes, belts and shoes and scrotal or labial edema often occurs. As the edema accumulates, pleural effusions, ascites and decreased urine output may develop. In many cases, there is a history of preceding upper respiratory symptoms. Anorexia, abdominal pain and diarrhea may be seen, possibly secondary to the formation of ascites. Blood pressure and renal function are usually normal.

The hallmark of nephrotic syndrome is severe proteinuria, most reliably diagnosed using a 24-hour urine collection. Spot urinalysis is also informative and reveals +3 to +4 proteinuria (300 to 1000 mg/dL), with a specific gravity usually greater than 1.020. Gross hematuria is not common. Blood samples show decreased albumin levels usually less than 2.0 mg/dL and elevated triglyceride and cholesterol levels.
Because of the hypoalbuminemia, hypocalcemia is often seen, with calcium levels less than 9.0 mg/dL. Usually the ionized calcium will be normal. Hyponatremia and hyperkalemia can be seen, with hyperkalemia developing in patients who are oliguric. Serum C3 levels are normal in cases of minimal change disease.

Diagnostic criteria

I. Clinical:
   1. Extrarenal symptoms:
      1. edemas - at first they occur on eyelids, face; later they may be generalized;
      2. arterial hypertension - more often hypertension is moderate, in some cases it may be absent.

   2. Renal symptoms:
      a) oliguria and anuria are present in the initial period of acute glomerulonephritis, in this case urine has high specific gravity (1030-1040 and more);
      b) hematuria of different degree – moderate (microhematuria) and massive (macrohematuria);
      c) proteinuria:
         • moderate - up to 1000 mg/l (daily loss is up to 1 g);
         • significant - more than 1000 mg/l, up to 2500-3000mg/l (daily loss is 2,5-3 g);
      - massive - more than 3000 mg/l (daily loss is more than 3 g).

   3. Metabolic symptoms:
      1. disorders of water-electrolyte metabolism, which are characterized by different types of hyperhydration – intracellular and extracellular; in ionogram there is elevation or decreased level of some electrolytes in plasma and erythrocytes. These disorders are most significant in acute glomerulonephritis in oligoanuric period, in the development of acute and chronic renal insufficiency;
      2. disorders of protein metabolism are the most significant in high proteinuria and they are characterized by hypoproteinemia (total protein level is less than 60 g/l), hypoalbuminemia (albumins are less than 50%), changes of globulin's fractions ratio;
      3. disorders of fat metabolism are present in some cases of glomerulonephritis and they are characterized by hypercholesterinemia (cholesterin is more than 5 mmol/l).

   Mentioned above renal and extrarenal symptoms and metabolism disorders are seen in different cases of glomerulonephritis in various combinations.

Differential diagnosis of glomerulonephritis is provided with pyelonephritis, renal tuberculosis, and tumor.

Glomerulonephritis lasting for 1 year and longer is regarded as to be chronic.

Treatment of Glomerulonephritis

Regimen - bed rest until restitution of diuresis, disappearance of extrarenal symptoms and decrease of blood pressure will occur, as usually bed rest lasts 2-3 weeks.

Diet. Limitation of salt and water is the main principle. Up to 4-5th weeks the diet is salt free, than 0,5 g/d of salt may be given for a patient, to the 8th week - 1,5 g/d, but quantity of salt shouldn’t exceed 3/4 of norm (norm is 50 mg/kg/d) during 1-2 years.

Daily quantity of liquid must be equal to diuresis, if information is absent - approximately 15 ml/kg
(400 ml/m²), that is imperceptible losses. Diet with protein's restriction is prescribed for patients with azotheemia: №7а during 3-5 days, №7b - 3-5 days, than -№7(1 mo). In oliguric phase restriction of potassium is necessary, in polyuric - vice versa. After diet 7 we prescribe diet 5 for 5 years.

Antibiotic therapy. Penicillin, erythromycin in therapeutic doses are indicated within 8-10 days. If there are foci of chronic infection, 3-4 cycles of antibiotics are expedient. It’s necessary to avoid nephrotoxic ones. Tonsillectomy usually is provided not earlier than 6-12 mo. after the onset of disease.

Membranostabilizers are also administrated (Tocoferol et al).

Vitamin therapy. Usual therapeutic doses of vitamins are used.

Improvement of renal blood flow - regimen with limitation of physical activities, electrophoresis with nicotinic acid or heparin, i.v. injections of euphyllin (2 mg/kg 3 times/day), trental (5 mg/kg 3 times/day), dipiridamol (5 mg/kg 3 times/day orally).

Management of edema - diuretics: lasix i.m. or i.v. 1-2 mg/kg in combination with hypothiazid (not in oliguric stage!) 0,5-1 mg/kg orally or amilorid 5 mg orally.

Management of hypertension - the 1th, 2nd and 3rd generation of renin-angiotensin-aldosterone system (RAAS) antagonists are used (captopril, cozaar). Initial dose is 0,25-0,5 mg/kg, then according to therapeutic effect. Calcium antagonists (nifedipin) single or as well as another antihypertonic drugs (methyldopha - 5-10 mg/kg orally) are prescribed.

If eclampsia occurs: lasix i.v. 2 mg/kg, papaverin with dibazol i.m., diazepam 0,3-0,5 mg/kg i.m. (not magnesium!).

In nephrotic forms glucocorticoids, in mixed and nonsusceptible forms combination of glucocorticoids with cytostatics are indicated.

Complete recovery may occur in 95% of patients with acute glomerulonephritis. Those with severe renal involvement may develop chronic renal failure. Recurrences are rare.

Prognosis is excellent for APSGN and variable for other causes of GN in children. Complications of AGN include acute renal failure, hyperkalemia, hypertension, volume overload (congestive heart failure, pulmonary edema, hypertension) and chronic renal failure.