

Primary idiopathic glomerulonephritis: modern algorithm for diagnosis and treatment*

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KEY WORDS

clinical presentation, epidemiology, glomerulonephritis, pathogenesis, treatment

ABSTRACT

In most countries glomerulonephritis is the second most common cause of the end-stage renal disease, after diabetic nephropathy in renal replacement therapy programs. Occurrence of primary glomerular diseases in young and middle aged patients, in whom they restrain their lives and professional careers, results in their particular position among causes of replacement therapy. A highly important component of the therapeutic approach to nephrotic patients is appropriate symptomatic treatment. Proteinuria reduction is crucial in the prevention of progressive kidney function decline in the course of glomerulonephritis. A long-term therapy of glomerulonephritis should be conducted both by the general internal medicine specialist and the nephrologist. The treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor blockers can be performed by the internist, but the immunosuppressive programs should be initiated and supervised by the nephrologist.

Epidemiology In most countries glomerulonephritis is the second most common cause of the end-stage renal disease (ESRD), after diabetic nephropathy in renal replacement therapy programs. In Poland, at the end of 2005, dialysis treatment was performed in 2839 patients who developed ESRD in the course of glomerulonephritis (22.25% of the total number of 12,759 persons, following diabetic nephropathy with 3072 patients, 24%).¹ Prevalence of primary glomerular diseases in young and middle age patients in whom they restrain their lives and professional careers results in their particular position.² In one of large registries of glomerulonephritis the mean age of patients was 34.5 ± 14.6 years. Data from different countries indicate that primary glomerulonephritis are accounted for 54.8–70.8% of all glomerulonephritis cases. According to data obtained from the Brazilian registry, the most common primary glomerular disease in the adult population is focal and segmental glomerulosclerosis (29.7%), followed by membranous nephropathy (20.7%), IgA nephropathy (17.8%), minimal change disease (9.1%), membranoproliferative glomerulonephritis (7%), and crescentic glomerulonephritis (4.1%).³

Pathogenesis, immunological mechanisms and genetic factors Immunological mechanisms are involved in the pathogenesis of most types of glomerulonephritis and encompass autoantibodies to glomerular antigens, immune complexes deposited from the circulation or formed in situ within the glomerulus. Glomerular inflammation, especially with an accompanying interstitial component is also triggered by cell-mediated immunity. 2 types of local reactions may occur as a result of the interaction of sensitized effect or T cells with antigens; delayed-type hypersensitivity initiated by antigen-specific T cells with macrophage recruitment in the effector phase, and direct injury caused by cytotoxic T cells binding to cellular surface antigens. In addition, cytokines released from distant lymphocytes or macrophages may act as permeability factors and mediate proteinuria. Various immunological mechanisms were convincingly demonstrated in experimental models of glomerulonephritis, but the findings are not so clear in human pathology of glomerulonephritis. The term “primary glomerulonephritis” means that principal abnormalities and clinical manifestations are restricted to the kidney, the addition of “idiopathic” reflects ignorance of the etiologic factor, whereas secondary glomerulonephritis, a renal manifestation of systemic diseases or its

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etiology is recognized as in post-infectious glomerulonephritis and in glomerulonephritis associated with malignancies. Glomerulonephritis mediated by autoantibodies includes antiglomerular basement membrane disease (Goodpasture's disease), lupus nephritis, Wegener's granulomatosis, and microscopic polyangiitis. The group of glomerulonephritis with immune deposits, but without a proven role of autoantibodies, consists of membranous nephropathy, IgA nephropathy, and mesangiocapillary glomerulonephritis. The proteinuria produced by permeability factors is implicated in minimal change disease and focal segmental glomerulosclerosis.⁴

A novel finding in the genetic background of glomerulonephritis is the discovery of gene mutations of the podocyte (cells forming the visceral epithelium of Bowman's capsule) and slit-diaphragm proteins in familial and some sporadic cases of focal segmental glomerulosclerosis in children and young adults.⁵ The list of mutated proteins encompasses the following structural podocyte components, including podocin, α -actinin 4, CD2-associated protein, and the latest advance, namely the transient receptor potential cation channel 6.⁶

Another novel achievement in the understanding of minimal change disease and focal segmental glomerulosclerosis pathogenesis has been the demonstration that the disease can be transmitted to a mouse model by progenitor stem CD34+ cells deriving from patients with minimal change disease. However, this effect could not be achieved by mature T CD34+ lymphocytes. It suggests that pathogenic lymphokine, also known as permeability factor, is produced by immature differentiating cells rather than by mature peripheral T cells.^{7,8}

In humans, glomerulonephritis can be exacerbated by bacterial and viral infections. Most recently, the mechanism of these relationships has been elucidated. An association appeared to be innate immunity, particularly the Toll-like receptor family localized among others on macrophages, dendritic cells, and neutrophils which are stimulated by bacterial and viral products.⁹

Clinical and pathomorphological presentation

The clinical spectrum of glomerulonephritis comprises:

- 1) asymptomatic subnephrotic proteinuria without hematuria
- 2) asymptomatic proteinuria with hematuria. The coexistence of asymptomatic proteinuria and hematuria substantially increases the risk of significant glomerular damage, hypertension, and progressive renal dysfunction in comparison to the situation of isolated asymptomatic proteinuria
- 3) nephrotic syndrome, i.e., proteinuria in excess of 3.5 grams in 24 hours, accompanied by edema, hypoalbuminemia, hyperlipidemia and lipiduria
- 4) nephritic syndrome: non-nephrotic proteinuria, hematuria with red-cell casts, hypertension

(secondary to sodium retention), appearing tendency to glomerular filtration rate (GFR) lowering

- 5) course of rapidly progressive glomerulonephritis, including non-nephrotic proteinuria, hematuria with rapid GFR decline and acute renal failure
- 6) macroscopic hematuria associated with glomerular diseases, appearing mainly in children and young adults, and rare after the age of 40 years, as a symptom of IgA nephropathy and postinfectious glomerulonephritis. The characteristic feature of IgA nephropathy is episodic frank hematuria occurring simultaneously with an upper respiratory tract infection, whereas in postinfectious glomerulonephritis there is a 2–3-week period of latency between infection and hematuria.

The clinical pattern of particular primary idiopathic glomerulonephritis is shown in [TABLE](#).

The data presented in the table clearly show that the clinical picture of the different glomerulonephritis types overlaps. Therefore, an appropriate diagnosis requires renal biopsy performance with sample evaluation by light microscopy, immunofluorescence or immunochemistry, and electron microscopy.

The principal investigations in glomerulonephritis patients encompass the quantification of the excreted protein amount, urine microscopy including the evaluation of erythrocytes, leukocytes, and casts. A necessary component represents also chemistry profile with serum creatinine levels and glomerular filtration rate (GFR) estimation; complete blood count; immunological tests: antinuclear antibodies, antineutrophil cytoplasmatic antibodies, antiglomerular basement membrane antibodies, total hemolytic complement activity; ultrasound kidney examination.

The cumbersome 24-hour urine collection for daily proteinuria can be replaced by the measurement of protein-to-creatinine ratio (mg/mg) on random urine. Protein excretion follows a circadian rhythm (highest during the day and lowest after a night's sleep). In a typical nephrotic patient, the urine protein/creatinine ratio at mid-day is approximately 1.7-fold greater than that in the morning. Therefore, in the follow-up, the spot sample for the protein/creatinine ratio should always be collected at the same time of the day. When in the spot urine the protein concentration is 400 mg/dl and creatinine concentration is 100 mg/dl, then the ratio amounts to 4, which indicates proteinuria of 4 grams per 24-hours.⁴

Principles of glomerular proteinuria management

A highly important component of the therapeutic approach to nephrotic patients is appropriate symptomatic treatment. A key element in nephrotic edema development is sodium retention due to an increase of tubular reabsorption. This is a secondary event in patients with the most severe nephrotic syndrome (serum albumin <2 g/dl), in whom edema appears to be the consequence

TABLE Clinical paradigms of individual forms of primary idiopathic glomerulonephritis

	Nephrotic syndrome	Nephritic syndrome
Minimal change disease	+++++	–
Focal segmental glomerulosclerosis	++++	+
Membranous nephropathy	++++	+
IgA nephropathy	+++	++
Membranoproliferative glomerulonephritis	++	+++
Crescentic rapidly progressive glomerulonephritis	+	++++

of the low serum albumin leading to a decrease in plasma oncotic pressure which results in increased transudation of fluid from capillary beds into the extravascular space and causes plasma volume diminishment (edema formation according to the underfill mechanism). In the majority of patients with less deep hypoalbuminemia, the increase of tubular sodium reabsorption is a primary defect and edema appear in the overfill mechanism in which elevated blood volume facilitates transudation of fluid into the extravascular space.⁴

Recent experimental studies have thrown new light on the cellular and molecular mechanisms of augmented sodium tubular reabsorption in nephrotic patients. It was shown that renal sodium retention results from enhanced sodium reabsorption along the connecting and cortical collecting ducts, as well as from blunted responsiveness of medullary collecting ducts to atrial natriuretic peptide. It was also documented that the induction of de novo synthesis of Na,K-ATPase is the primary effector of increased sodium reabsorption. Amiloride, an inhibitor of a conductive sodium channel in the distal tubule, can ameliorate this increased sodium reabsorption.¹⁰

As it was already mentioned, whatever their etiology, nephrotic syndromes are always associated with renal retention of sodium. Therefore, the mainstays of nephrotic edema treatment are diuretics accompanied by moderate sodium restriction (60–80 mmol/24 h). In severely edematous patients loop diuretics, e.g. furosemide, is preferred. Loop diuretics, including furosemide, exhibit a high degree of protein binding of >95%. In nephrotic syndrome, hypoalbuminemia diminishes the amount of albumin bound furosemide that can interact with the anion transporter and as a consequence, diminishes the furosemide delivery to its site of action which is the ascending Henle loop. In consequence, higher doses of furosemide (80–200 mg) are effective in nephrotic patients, initially administered by intravenous route. In mild and moderate edema, thiazides, amiloride, and spironolactone represent a sufficient therapeutic approach.⁴

In the prevention of progressive kidney function decline in the course of glomerulonephritis, proteinuria reduction is crucial. A study using the

angiotensin-converting enzyme inhibitor (ACEI), ramipril, showed that for each 1 g/24 h reduction observed at the 3rd month of therapy, subsequent GFR decline was slowed by about 2.0 ml/min per year. In most proteinuric kidney diseases, GFR loss occurs at about 4 to 10 ml/min per year. Thus, proteinuria reduction of 1.0 g/24 h or more significantly prolongs time to ESRD. A number of studies have showed that a progressive loss of renal function is prevented when proteinuria is reduced to level <0.5 g daily, and in fact does not occur when proteinuria is lowered to <0.2 g daily.

The antiproteinuric therapy is based on the renin-angiotensin-aldosterone system inhibition ACEI and(or) angiotensin receptor blockers (ARB). The optimal doses are higher than in antihypertensive treatment. Both ACEI and ARB usually reduce proteinuria independent of blood pressure. This substantiates therapy in normotensive patients with proteinuria. In hypertensive patients, the goal is low blood pressure $\leq 120/75$ mmHg, with a further dose increase if tolerated. There is now clear evidence that the combination of ACEI/ARB therapy reduces proteinuria to a larger extent than either drug alone.¹¹ The benefits resulting from a double blockade are shown in the COOPERATE trial, in which trandolapril (3 mg/24 h) and losartan (100 mg/24 h) reduced proteinuria by 40%, while simultaneous administration resulted in a 76% reduction, associated with a significantly more beneficial effect on GFR.¹² Doses of ACEI and ARB should be increased slowly to prevent symptomatic hypotension.

To obtain the complete antiproteinuric effect of the renin-angiotensin-system inhibition, a two-month treatment is needed. That allows to select patients who can most benefit from anti-inflammatory and immunosuppressive therapy. To induce remission in patients with glomerulonephritis, glucocorticosteroids and cytostatics (cyclophosphamide, chlorambucil, azathioprine) are used, as well as anti-rejection drugs transposed from renal transplantology, including cyclosporine, tacrolimus, and mycophenolate mofetil. The programs of anti-inflammatory and immunosuppressive treatment, which are different in the particular morphologic types of glomerulonephritis, should be implemented and supervised by nephrologists. Their detailed overview is beyond the scope of this paper.

SUMMARY The long-term therapy of glomerulonephritis should be conducted both by the general internal medicine specialist and the nephrologist. The patient with subnephrotic proteinuria and(or) hematuria may be cared for by an internist after consultation with a nephrologist. Nephritic syndrome with a tendency to GFR decrease and nephrotic syndrome require the immediate referral to the nephrologist. Treatment with ACEI and ARB can be performed by the internist, but the immunosuppressive programs should be initiated and supervised by the nephrologist.

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