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Etiopathogenetic, Morphological, Diagnostic and Therapeutic Aspects of Acute Glomerulonephritis: Current Status

Abstract

This review provides current information on etiological factors and pathogenetic mechanisms of development, morphological changes, clinical and laboratory manifestations of acute glomerulonephritis, as well as possible therapeutic management thereof. Epidemiological issues concerning acute post-streptococcal glomerulonephritis are discussed, including characteristics of the effect of nephritogenic strains of streptococci. Immunopathological reactions of the body with acute glomerulonephritis to the causative agent of the disease and its antigens are shown, with the development of an imbalance of T cell subpopulations, nephritogenic potential of streptococcal proteins, the marker of active proliferation of mesangiocytes, C3 and C4 fractions of complement, as well as the renin-angiotensin-aldosterone system. This article emphasizes the fact that the value of serological test results with underlying acute glomerulonephritis increases with the simultaneous estimation of complement C3 and C4 fractions. The article presents pathological effects of angiotensin II and aldosterone on renal tissue with the transition of acute glomerulonephritis into chronic form, the development of nephrotic proteinuria and rapid decrease of renal function. Information on the direct correlation between the severity of histological changes and clinical signs of acute glomerulonephritis and, possibly, the prognosis is presented. Up-to-date information on the assessment of the primary clinical signs of acute glomerulonephritis (urinary syndrome, edema syndrome and hypertension) is provided. When discussing the management of acute glomerulonephritis, controversial issues concerning antibiotic treatment and prophylactic tonsillectomy were noted. Literature data on management options for edema syndrome and hypertension with the use of thiazide and loop diuretics, calcium antagonists, beta blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers are provided. Issues concerning immunosuppressive treatment with glucocorticoids, as well as prognostic criteria for acute glomerulonephritis, are discussed.

Key words: *acute glomerulonephritis, nephritogenic streptococcal strains, influenza, hantavirus, complement fractions, arterial hypertension, edema syndrome, macrolides, glucocorticoids*

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ACE inhibitors — angiotensin-converting enzyme inhibitors, AGN — acute glomerulonephritis, AH — arterial hypertension, APIGN — acute post-infectious glomerulonephritis, APSGN — acute post-streptococcal glomerulonephritis, AT — angiotensin, BP — blood pressure, CKD — chronic kidney disease, GCS — glucocorticosteroids, HD — hemodialysis, NS — nephrotic syndrome, RAAS — renin-angiotensin-aldosterone system, SSRN — Scientific Society of Russian Nephrologists

Introduction

The term «glomerulonephritis» is a general one and is associated with immune inflammation and the development of morphological changes with the proliferation of cell elements in glomeruli. The adjective «acute» (acute glomerulonephritis (AGN), acute post-streptococcal glomerulonephritis (APSGN)) indicates the time frame of disease that is often used in clinical practice, and in most cases has definite clinical and pathological correlations. These terms also imply the presence of a number of typical features related to the etiology, pathogenesis, course and prognosis of this disease. AGN is primarily an immune complex-mediated lesion of the glomerular apparatus that is caused by infectious or non-infectious agents [1–3]. AGN is one of the forms of glomerulopathy, which is characterized by the sudden development of hematuria, proteinuria, arterial hypertension (AH), and edema, in some cases with transient renal dysfunction, in combination with the morphological picture of acute diffuse proliferative glomerulonephritis. The immune-inflammatory process with underlying AGN develops in glomeruli and results in characteristic structural and clinical manifestations.

Etiopathogenesis and Morphological Changes

Streptococci play a leading role in the development of AGN, a fact which is reflected in the other name for this disease — APSGN. Acute immune complex-mediated diffuse proliferative glomerulonephritis, which is often associated with infectious diseases, is referred to as acute postinfectious glomerulonephritis (APIGN). Besides streptococci, AGN may result from other infections (bacterial, viral, parasitic). Although any viral infection can lead to the development of immune complex-mediated proliferative glomerulonephritis, several groups of pathogens deserve discussion due to the special pathogenetic mechanism that results in kidney damage. In addition to the well-known pathogens of influenza, measles, rubella, hepatitis A and B, recent years have seen the extensive study of the role of dengue virus, hantavirus, parvovirus-B19, Epstein—Barr virus, cytomegalovirus and many others in the origin of AGN [4, 5]. AGN is reported during influenza and hepatitis A epidemics. In Africa and Asia, AGN can be caused by parasitic infections (tropical malaria, schistosomiasis) [6–8].

The most common clinical picture of AGN is observed when the disease is caused by group A beta-hemolytic streptococcus. AGN is an urgent issue due to diagnostic difficulties, imperfect therapy, and poor prognosis for some variants of its clinical course [2]. AGN is usually characterized by various clinical manifestations in conjunction with the morphological picture of proliferative glomerulonephritis. It should be noted that young people under the age of 40 years are more likely to suffer AGN [1–3], with the peak incidence of the disease occurring at a very young age — from 5 to 12 years. However, the risk of developing this disease, its complications, as well as poor prognosis also persists among elderly patients [9–11].

By the World Health Organization's estimates, AGN is widespread in developing countries, where the prevalence of streptococcal infection is relatively high [12]. Every year, 470 thousand cases of AGN caused by streptococcal infection are registered all over the world; 400 thousand of said cases are reported among the pediatric population [13]. The results of a recent study showed a high incidence of AGN among disadvantaged children [14]. The study conducted by M. Sharmin et al. (2020) analyzed socio-demographic features of the clinical profile and outcomes of AGN in hospitalized children living in rural areas [15]. Skin streptococcal infection was the most common cause of AGN [15]. Currently, recovery is a relatively rare outcome of AGN [1]. According to N. A. Mukhina et al. (2015), a relatively new attribute of AGN today

is its possible development as a «second» renal disease with underlying chronic kidney disease (CKD) with the development of nephrotic proteinuria [1]. There are reports of post-streptococcal AGN in a 45-year-old man with a kidney transplant [16]. In some cases, AGN morphs into subacute glomerulonephritis and progresses to terminal renal failure [9]. Implementation of intravital renal biopsy revealed the nature of several morphological types of glomerular apparatus lesions related to glomerulonephritis [3, 9]. Results of current clinical and morphological studies formed the basis of international recommendations on AGN [17, 18].

The list of infectious agents that can cause AGN is now longer [1]. A case of AGN in a three-year-old girl with respiratory symptoms after chlamydial pneumonia was reported [19]. In 2013, K. V. Kanodia et al. described a rare case of malaria Plasmodium vivax in a 28-year-old woman, which was complicated by AGN [20]. Histological findings revealed increased mesangium, segmental endocapillary proliferation, as well as severe infiltration with neutrophils and lymphocytes [20]. AGN can occur as epidemic outbreaks caused by nephritogenic strains of group A streptococci [21, 22]. This is confirmed in the description by S. Baiter et al. (2000) of 253 cases of AGN reported from December 1997 to July 1998 in the state of Nova Serrana, Brazil [23], when the incidence of this pathology was 18 cases per 1,000 of population. During this outbreak, seven patients required hemodialysis (HD), and three patients died [23]. It is worth noting that said AGN epidemic was caused by Streptococcus zooepidemicus (Lancefield group C streptococci), which was isolated for the first time in 1934 by P. R. Edwards and was named Animal pyogens A [24]. This conventionally pathogenic microorganism of mucous membranes affects animals and humans [24]. AGN problems associated with streptococcal infection were detailed in an analytical study by B. Rodriguez-Iturbe et al. (2007) [25]. It should be noted that in susceptible individuals, type 1, 4, and 12 streptococcal strains cause AGN after inflammatory lesions of pharyngeal mucous membrane and lymphoid tissue [18]. In primary and secondary streptococcal pyoderma, where the incubation period is 7–10 days, the disease may result from the action of nephritogenic type 2, 49, 55, and 57 streptococcal strains [18]. It is believed that when the disease is caused by type 49 streptococci strain, the risk of developing AGN due to skin infection is several times higher than with pharyngitis [26, 27]. According to some studies, the 12th streptococcal strain is found in 60–80% of patients with AGN [3].

In some cases, AGN develops as a result of vaccination, chemical poisoning, or consumption of food containing preservatives [1, 3, 28, 29]. Cases of AGN in children after vaccination were described; renal biopsy revealed deposits consisting mainly of immunoglobulin (Ig) A and C3 complement that were located in the capillary wall of glomeruli and the mesangium [11, 30]. Post-vaccination AGN based on complex mutations of C2 complement in 70–75% of cases develops after the second or third vaccine injection [3, 30, 31].

When examining the etiopathogenetic aspects of AGN using the example of streptococci, it is essential to highlight several mechanisms mediated by immunological processes. For APSGN, the damaging role of immune complexes, which include specific antibodies against streptococcal antigens, was proven [18]. These immune complexes are localized in the wall of glomerular capillaries and are activated by the complement system [6, 7]. The immune system can also be triggered by streptococcal antigens that bind to different glomerular structures and act as «embedded antigens» or by transformation into endogenous antigens. Upon activation of the complement cascade, chemotactic plasma-activated C5a protein and inflammation mediators of platelet origin are formed [8]. Different types of cytokines and other immune factors trigger an inflammatory response, which manifests as cell proliferation and swelling of the glomerular vascular bundle [6].

Taking into account the fact that a high incidence of AGN is registered in cases of infectious diseases, clinicians should keep in mind the primary stages of the epidemic process addressed in the writings of academician Lev Vasilievich Gromashevsky, the author of the systematic epidemiologic theory, who introduced the concept of infection source and driving force of epidemic [32]. The most common serotype of group A beta-hemolytic streptococci associated with nephritis due to nasopharyngeal infections is type 12. Type 49 is more often detected during outbreaks of APSGN associated with pyoderma with underlying streptococcal impetigo (the foci are mostly on the body, upper and lower extremities, and the face), streptococcal intertrigo (inguinal region, intergluteal cleft, axillary folds and retroaural folds), bullous impetigo (inflammation mainly on the hands, feet and legs),

streptococcal ecthyma (mainly on the extremities and buttocks) [33, 34]. The scratching of infected areas and contact with water and other objects contribute to the spread of streptococcal pyoderma [33, 34]. Furthermore, streptococci can be transmitted through household items. They enter the human body through damaged skin or with food [33, 34]. For instance, cheese made from low-quality milk caused an outbreak of AGN in the state of Nova Serrana (Brazil), and a ban on sales of this low-quality cheese helped stop the epidemic [23]. The risk of AGN transitioning into chronic form is very high in adults infected with atypical strains of streptococci [35]. Epidemic outbreaks of tropical malaria also contributed to the development of AGN [36]. AGN caused by streptococci more often develops during winter, 10–12 days after infection (pharyngitis, tonsillitis, scarlet fever) or acute viral contamination of the respiratory tract [1–3].

Predisposing factors, such as a family history of infectious and allergic diseases, high family susceptibility to streptococcal infection, chronic foci of infection, hypovitaminosis, helminthoses, etc., are of importance in the development of AGN. [7]. Genetic analysis of streptococci obtained during epidemic outbreaks of AGN indicates a rapid and unpredictable variability of this microorganism thanks to which its new strains acquire nephritogenic properties [1, 18]. During the analysis of typing of 68 isolates of group A streptococcus associated with AGN outbreaks in patients aged 4 to 17 years in two neighboring provinces of China, Chinese scientists identified 11 different emm types of group A streptococcus [37]. Analysis of the distribution of emm types revealed that AGN outbreaks in these two provinces were caused by emm 60.1- and emm 63.0-type group A streptococcus. Among 68 isolates of group A streptococcus, 88.2% and 97.1% were resistant to erythromycin and tetracycline, respectively [37]. In fact, this study is the first report about the nephritogenic strain M-63 of group A streptococcus [37].

In a study conducted by T. Abraham et al. (2018), 206 isolates of group A streptococcus obtained from different clinical samples (streptoderma, pharyngitis, osteomyelitis, etc.) from November 2013 to October 2017 were analyzed [38]. Men (62%) dominated this study population, in comparison with women (38%). It was found that most of the erythromycin-resistant isolates (63%) belonged to the iMLS phenotype, followed by the M phenotype (37%) [38]. The study by A. Muhtarova et al. (2019) of 102 macrolide-resistant group A streptococcus strains obtained in 2014–2018 showed emm 28 (22.55%), emm 12 (17.65%) and emm 4 (16.66%) as the most common types [39]. In the transition of AGN into chronic forms, the imbalance in T cells subpopulations plays a leading role.

According to S.I. Ryabov et al. (2013), the mechanism of glomerular pathology should primarily be associated with the genetic inferiority of T cell immunity, which ultimately results in the breakdown of the repair processes of certain parts of the nephron with further changes in the antigenic structure thereof and the formation of immune complexes [40]. Currently, the deposition of antigens of nephritogenic strains of streptococci in the glomeruli and their binding to antibodies with the formation of immune complexes in situ and the activation of the complement system is considered the primary pathogenetic mechanism of AGN [1, 18].

Current data show no direct damage to kidneys by an infectious agent in case of AGN. The disease is caused by the pathological immune response to the pathogen and its antigens. That is why the first signs of the disease with the "classical" course of AGN appear 1–3 weeks after streptococcal or viral infection when the body becomes susceptible to the antigens of the microorganism [1, 3]. After penetrating the mucous membrane of the upper respiratory tract, streptococcus triggers an infectious process in the nasopharynx. Streptococcus isozymes with toxic and antigenic properties, in particular streptolysins O and S, as well as streptokinase, proteins, deoxyribonuclease B (DNase B), etc. also play an important role in the development of inflammation and tissue damage [3]. The streptococcal cell membrane contains M-protein, which possesses antigenic properties. This factor increases streptococcal resistance to phagocytosis. Group A streptococci and cardiomyocytes have a similar antigenic structure, which leads to immunological response against streptococcal components as well as myocardial sarcolemma and cardiac valvular glycoproteins [3, 6, 18]. Streptolysins O and S lyse tissue cells, which causes the fixation of immune complexes in organs. In cases of AGN resulting from nephritogenic strains of group A streptococci, endostreptolysins, that have a significant affinity for glomerular structures, are produced [2, 3]. When endostreptolysins appear in the bloodstream, they bind to glomerular sites, which results in complement activation and the formation of immune complexes with subsequent damage to the

glomerular capillary endothelium [17, 18]. At the same time, in cases of AGN, the hemostasis system is activated, and local intravascular coagulation develops with the formation of microthrombosis in glomerular capillaries [41]. The number of mesangiocytes that produce α-smooth muscle actin steadily increases as the duration of the disease increases [42]. Mesangium is infiltrated with neutrophils and monocytes, while neutrophils contribute to the production of cytokines, which increases the flow of other cell elements into the mesangial region [25]. Glomerular damage in case of AGN is also due to neuraminidase of streptococci that are deposited in intact glomeruli and bind to anti-IgG antigens, followed by the formation of immune complexes that damage renal tissue [42]. The role of M-type membrane antigens, endotoxin D, erythrogenic exotoxin B and toxins of β-hemolytic streptococci was established in the pathogenesis of AGN when proliferation mechanisms are triggered in glomeruli and the complement C3 fraction is activated [4, 6, 42, 43].

The renin-angiotensin-aldosterone system (RAAS) is simultaneously activated, which results in sodium and water retention and vasoconstriction of renal arterioles [1, 17, 18]. Angiotensin (AT) II, with its strong vasoconstrictor and antinatriuretic effect, contributes to the active apoptosis of glomerular cells, primarily, mesangiocytes and endotheliocytes [6, 8]. T. Oda et al. (2007), having analyzed the results of renal biopsy obtained 1–31 days after the onset of the disease caused by streptococcal infection, found, in 15 patients with AGN, active apoptosis of glomerular cells, primarily, mesangiocytes and endotheliocytes [42]. On the other hand, in cases of AGN, apoptosis of podocytes is also triggered as a result of AT II intrarenal hyperproduction [1, 17, 18], which, in turn, results in the loss of podocytes with subsequent activation of epithelial-mesenchymal transdifferentiation mechanisms [44]. Podocytes lose the normal cytoskeleton structure, cell polarity, and cell junctions. Podocytes become mobile, which results in their increased desquamation from the basement membrane and podocyturia [43, 44]. Transdifferentiated podocytes, like fibroblasts, acquire the ability to produce matrix proteins (fibronectin, collagen, etc.), accelerating AGN transition into chronic form and glomerulosclerosis [45]. In addition, podocytes express mineralocorticoid receptors required for interaction with another RAAS component — aldosterone, which raises the risk of AGN transitioning into chronic form [46, 47]. When exposed to AT II, podocytes also produce proinflammatory cytokines with subsequent formation of nephrosclerosis [46]. This information can well explain proteinuria rising to the nephrotic level and the rapid decrease in renal function in some variants of the course of AGN [1, 3, 19, 20].

Thus, the above-mentioned pathogenetic mechanisms result in progressive failure of renal function with a decrease in glomerular filtration and a decrease in salt and water excretion, which leads to edemas, AH, anemia and symptoms of encephalopathy [8–10]. According to clinical and practical recommendations of the Scientific Society of Russian Nephrologists (SSRN), morphological diagnosis of AGN is based on the results of light and electron microscopy, as well as on immunofluorescence assay of kidney biopsy [17, 18, 48]. Light microscopy shows the enlargement of glomeruli, narrowing of their lumen due to proliferation of mesangial cells, increased thickness of mesangial matrix, a large number of neutrophilic leukocytes, and the narrowing of the lumen of glomerular capillaries [48, 49]. The pattern of endocapillary proliferative glomerulonephritis characterizes APSGN [47, 50]. Electron microscopy reveals hump-type subepithelial deposits (immune complexes). Crescent formation in AGN is considered to indicate an unfavorable prognosis [49, 50]. A typical sign in immunofluorescence assay is finding granular deposits of immunoglobulin G and C3 complement in the mesangium and glomerular capillary walls [49, 50]. A direct correlation was established between the severity of histological changes and clinical signs of AGN and, possibly, the prognosis. [49, 50]. The morphological pattern of an acute process is generally considered as endocapillary diffuse proliferative glomerulonephritis that can have several stages — exudative, exudative-proliferative, proliferative and the stage of residual effects that can persist for several years [51].

Clinical Picture

Urinary syndrome, edemas and AH usually accompany AGN [1, 3]. The development of edemas with underlying AGN can be explained by decreased filtration rate due to glomerular damage and sodium retention [52, 53]. Furthermore, edemas in case of AGN are associated with changes in RAAS activity [6, 7, 48] and a high level of atrial natriuretic peptide [1]. It is believed that in cases of AGN, there is increased tubular reabsorption of water and sodium in the

distal nephron due to a number of endothelial and mesangial factors [2]. Interestingly, these changes develop regardless of the antidiuretic hormone and aldosterone [9]. Severe AGN is often accompanied by transient oliguria [1]. Generalized edema develops more often in children than in adults [13]. Due to the swelling of the renal parenchyma, lumbar pain is reported in 10–50% of AGN cases.

One of the most common signs of AGN is high blood pressure (BP). The main reasons for AH in case of AGN are increased circulating blood volume associated with sodium and fluid retention, as well as increased cardiac output and peripheral vascular resistance [1, 2, 18]. Significant increase in BP occurs in more than 75% of patients. AH is usually most significant at the height of the disease, and BP gradually normalizes when urine output increases [1, 54].

Clinical signs of AGN may vary; subclinical forms with isolated changes in urine test results are reported [11, 55]. According to current data, the detection of three or more RBC, i.e., hematuria, in the field of vision is considered a mandatory sign of AGN; about 30–50% of patients have gross hematuria, while others have microhematuria [13]. Crucially, the detection of more than 70% of abnormal RBC usually indicates the glomerular origin of hematuria [3, 48]. It is believed that if an outbreak of streptococcal A infection is caused by nephritogenic strains, then 3–15% of infected individuals contract AGN, although around 50% of those close to a patient with AGN have signs of urinary syndrome, i.e., they are likely to have low-symptomatic (monosymptomatic) variants of AGN [1, 3]. The abovementioned M. Sharmin et al. study (2020) demonstrated that hematuria and AH are common clinical signs in patients with AGN [15].

In the case of AGN, proteinuria may have varying degrees of severity. Nephrotic-level proteinuria may be found in adults [1]. At the early stage of AGN, a high level of immune complexes and low level of C3 are detected in blood serum along with normal ranges of complement C1, C2, and C4 fractions [18]. This confirms the predominant effect of alternative ways of triggering the complement system. Therefore, a decrease in complement C3 occurs with an underlying normal level of C4 and is considered typical for streptococcal AGN. The decrease in C3 in AGN is registered in more than 90% of cases [56, 57], although the decreased level itself is not pathognomonic for APIGN [57]. A low level of complement C3 occurs even several days before AGN develops and persists for 4–8 weeks [13]. Notably, in some patients, C4 and C2 fractions are also decreased, which indicates complement activation in both the classical and alternative ways [57]. Therefore, it is the simultaneous assessment of complement C3 and C4 fractions that increases their diagnostic value [13]. The course of AGN depends on the peculiarities of systemic pathological immune responses. It was established that the presence of autoantibodies against the complement C1q fraction, coupled with a decrease in C1q and C3 fractions in serum, is associated with significantly higher proteinuria, azotemia, as well as a higher incidence of oliguria, AH and protracted disease [58]. The role of serological changes and the activity of streptococcal membrane antigens in cases of streptococcal pyoderma is described in detail in the published work of T. Parks et al. (2015) [59]. In particular, an increase in serum titers of antistreptococcal antibodies in the case of AGN is one of the criteria indicating recent infection [60]. In cases of streptococcal skin infection, there is often no increase of antistreptolysin O titer because skin lipids prevent streptolysin from entering systemic circulation [61]. An increase in the concentration of anti-DNase is recorded with underlying AGN caused by streptococcal pharyngitis and pyoderma [58]. It is worth noting that the development of AGN may depend on different streptococcal antigens in different geographical areas and patients [25]. Consequently, the value of serological tests in cases of AGN caused by streptococci varies depending on the region and the degree of urbanization [3, 6].

In clinical practice, in cases with no positive trends, the persistence of hematuria and/or AH for more than four weeks, and the absence of documented evidence of previous streptococcal infection, AGN should be differentiated with IgA-associated nephropathy, proliferative membrane glomerulonephritis, secondary glomerulonephritis, hemorrhagic vasculitis, etc. [1, 3, 17, 18]. With typical clinical and laboratory manifestations and confirmation of previous streptococcal infection, AGN diagnosis is unmistakable in most cases.

Treatment

When discussing the treatment of AGN patients, N.A. Mukhin et al. (2015) note that the administration of antibacterial drugs in the absence of foci of active infection, and the use of pentoxifylline, as

well as preventive tonsillectomy, with no evidence of their effectiveness, are often accompanied by numerous adverse effects [1]. Therefore, the choice of the treatment method for AGN should be based on the consideration of the peculiarities of the disease course and symptoms that prevail in the clinical findings [1]. The beginning of antibiotic therapy for APSGN improves the primary consequences of this disease (i.e., edema syndrome, AH, hyperkalemia and renal clearance disorders). As mentioned earlier, these consequences are at the early stages of the disease and tend to be short-term, although with varying intensity. Therefore, patients may need frequent (daily or every other day) repeated assessments of clinical and laboratory data for their monitoring.

An immediate nephrology consultation is justified for patients with a creatinine level 50% higher than the norm or continuing to increase, with blood pressure (BP) higher than the 99th percentile by age and height, or with concomitant cerebrovascular pathology. Patients in the acute phase of the disease require bed regime and rest. As edema disappears and BP normalizes, regime may be changed. [60]. Timely antibacterial treatment for streptococcal infection can help ease nephritis and prevent the spread of the infection. In developing countries, where APSGN is common, prophylactic antibiotic treatment of people at risk effectively curbed the spread of nephritogenic strains of streptococci during endemic and epidemic periods [60]. There are reports of successful treatment of APIGN with antibacterial drugs only [62, 63]. Although early treatment with antibiotics theoretically reduces the total time of exposure to the streptococcal antigen, and subsequently, immunological response, it was not proven to prevent the development of APSGN. A Cochrane review covering 17 studies on the effectiveness of the treatment of streptococcal tonsillopharyngitis and the prevention of complications, including APSGN, showed the beneficial effect of antibiotic therapy. However, the number of cases was too small to consider this relationship as statistically significant [64]. Likewise, studies comparing the efficacy of different cephalosporins (results of a 5-day course) with the conventional 10-day course of penicillin showed no differences in the incidence of APSGN. Therefore, there is no obvious evidence indicating that timely antibiotic treatment of streptococcal infection is crucial for preventing APSGN [60].

Since edemas and AH in cases of APIGN have a common origin, their initial treatment should include, to some extent, limited fluid and sodium intake along with increasing urine output. Thiazide diuretics can be effective first-line drugs while loop diuretics should be considered for patients with more significant edema or, to some extent, with decreased renal function to ensure efficacy, since thiazides are not so effective with glomerular filtration less than 30 mL/min. However, the use of potassium-sparing diuretics should be avoided due to the existing risk of hyperkalemia in cases of APSGN. Loop diuretics reduce BP more effectively than other antihypertensive agents [17, 48]. If tighter control of BP is required, calcium channel blockers or β-blockers may be considered. Calcium channel blockers can cause fluid retention and edemas. Therefore, these agents should not be the only drugs used for treatment; they are likely to be effective in combination with diuretics. Angiotensin-converting enzyme inhibitors (ACE inhibitors) and AT II receptor blockers are often considered with caution in patients with APSGN. Theoretically, they may not be that effective in fluid overload cases because these patients have low serum renin and aldosterone levels. However, intrarenal renin levels are likely to be high in patients with reduced glomerular capillary perfusion. Studies demonstrated that patients treated with ACE inhibitors allowed better BP control and prevention of cardiac complications than when other antihypertensive agents, including loop diuretics, were used [48]. However, concerns over the possible deterioration of glomerular filtration and the development of hyperkalemia during the use of these agents require careful monitoring of clinical evidence and laboratory findings. Therefore, thiazide and/or loop diuretics remain the basic agents for controlling BP in patients with APSGN. Hyperkalemia is usually managed by temporarily limiting food intake, along with diuretics. Potassium-binding resins, such as sodium polystyrene, can also be considered, but they are a source of high sodium load for patients. Uncontrolled hyperkalemia, the volumetric overload of the left ventricle, and rapid increase in blood creatinine — are all indications for HD.

According to SSRN recommendations, oral glucocorticosteroids (GCS) are indicated for nephrotic syndrome (NS) that persists for more than two weeks, steadily rising creatinine level (with no tendency for further increase and normalization), and in cases when a renal biopsy cannot be performed [48]. There are several reports of successful treatment in cases of resistant APSGN with

GCS without any infection recurrence [59, 61]. For patients with sufficiently pronounced symptoms and indications for renal biopsy, intravenous administration of high doses of corticosteroids can be considered, especially if there is histological evidence of severe acute inflammation. Treatment with ultrahigh GCS doses is indicated if crescent formation is present in 30% of glomeruli in a renal biopsy sample and/or rapidly progressing glomerulonephritis [48]. However, there is no evidence that immunosuppression with GCS is useful for the treatment of AGN even in more severe cases. There are several reports of successful treatment in cases of resistant APSGN with GCS without any infection recurrence [59, 61]. The role of steroids in these patients can be attributed to the pathogenetic features of APSGN, including the interaction of the host immune system with the bacterial antigen. The advantages of GCS in terms of the quality of life and reducing the risk of HD treatment can be considered significant if the patient had NS and a tendency to decreasing renal function [48].

Prognosis

With respect to the prognosis in cases of APSGN, it should be noted that despite the limited treatment capabilities, the general prognosis for the disease is quite favorable. Volume overload and development of edemas are resolved quickly, usually within 10 days, and serum creatinine level returns to the baseline within 3–4 weeks. Any associated proteinuria often tends to decrease until it disappears completely, while microscopic hematuria can persist from several months to several years. Recurrences of APSGN are extremely rare, although there have been such cases, primarily in individuals with streptococcal skin infection due to different nephritogenic strains. Mortality rates associated with APSGN vary from 0.02 to 0.4 cases per 100 thousand, according to reports from developing countries, while deaths in developed countries are extremely rare. Mortality in these patients is usually caused by complications associated with volume overload and heart failure [64].

Long-term results of the prognosis for APSGN were initially considered to be satisfactory with a very small portion of patients with any persistent consequences during 5–10 years. Nevertheless, over the past decade, the results of a ten-year prognostic observation with slightly different results were analyzed. Persistent hematuria or proteinuria were found in 5–20% of patients with APSGN. AH was observed in 3% of patients, azotemia — in less than 1% of cases. The absence of changes in the level of complement C3 and C4 fractions, signs of NS and a predominance of crescent formation according to renal biopsy are believed to be the predictors of an unfavorable long-term prognosis [64].

Conclusion

Today, a lot remains unclear in the pathogenesis of AGN, since the number of infectious pathogens is steadily increasing, the range of human sensitization is widening, and the frequency of administration of vaccines and sera is increasing, which can lead to the development of this disease. The latent period between contracting streptococcal infection and the development of AGN is a characteristic feature of APSGN; this period ranges from 1 to 2 weeks with nasopharyngeal or from 2 to 6 weeks with skin localization of nephritogenic strains of streptococci. The study of the level of complement C3 and C4 fractions may be useful in the diagnosis of the streptococcal etiology of AGN. The most effective treatment for AH and edemas in patients with APSGN is loop or thiazide diuretics, which can also help reduce hyperkalemia. ACE inhibitors or AT II receptor blockers are considered effective agents for controlling BP, but they can result in hyperkalemia and temporarily affect the restoration of renal function. Despite the favorable prognosis of AGN, deterioration is observed with a decrease in complement C3, signs of NS and the prevalence of crescent formation in a renal biopsy sample.

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