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Research Article

IgA Nephropathy with Proteinuria and Renal Dysfunction - a

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ABSTRACT

IgA Nephropathy (IgAN) is the most common primary glomerulonephritis and a leading cause of chronic kidney disease and renal failure. Environmental and genetic factors play a role in the pathogenesis of IgAN. The immunopathogenesis of this disease is described as a multi - "hit" process. Renal biopsy is required for diagnosis. The immunofluorescence staining is characterized by a dominant IgA deposition. It is often clinically presenting with hematuria. In IgAN patients, proteinuria and renal dysfunction are less common. Conservative treatment, corticosteroids and immunosuppressives are commonly used in the treatment of IgAN.

Keywords: IgA nepropathy; Proteinuria; Treatment

INTRODUCTION

IgA Nephropathy (IgAN) is a common type of glomerulonephritis among primer glomerulonephrites. IgAN is an important cause of chronic renal disease and end-stage renal insufficiency. Initial manifestations of IgAN are recurrent episodes of gross hematuria that usually arise after upper respiratory tract infections. Clinically asymptomatic microscopic hematuria and / or mild to moderate proteinuria are seen. Rarely, nephrotic proteinuria or acute kidney failure may occur [1]. Nephrotic proteinuria during the diagnosis was seen severe glomerular injury and poor renal survival [2]. The 10, 20, and 30 years of renal survival rates were 84%, 66%, and 50%, respectively [3].

EPIDEMIOLOGY

The frequency of IgAN varies according to the geographical region. In European studies, IgAN was most commonly detected among primary glomerulonephritis. In Spain, IgAN was detected most commonly in adults with 17.2% and in children with 19.5% [4]. In the registry of the Czech Republic, IgAN was found to be the most common among the primary glomerulonephritis with 34.5% [5]. In the study conducted in Turkey, the most common cause of primary glomerulonephritis was detected as membranous glomerulonephritis (28.8%) followed by focal segmental glomerulosclerosis (19.3 %) and IgA nephropathy (17.2 %) [6].

In Asian countries, IgAN is more common. In studies conducted in China, IgAN (27.6-45.2%) was found as of the most common primary glomerulonephritis [7,8]. According to Japan data, IgAN as the most common cause of primary glomerulonephritis was found to be about 48% [9]. In a single-centered study of South Korean adults, IgAN was most frequently detected (33.3%) after mesangial proliferative glomerulonephritis [10]. In America and Brazil, focal segmental glomerulosclerosis is the most common type of primary glomerulonephritis. In the USA, the incidence of IgAN is 5-10% [11,12]. IgAN in renal biopsies are less common than 5% in the Central Africa [13].

Although IgAN is seen in all ages and both genders, it is more common in adolescents and young adults. It is more common in male gender. (Male to female ratio is 2: 1 or 3: 1) [14].

PATHOGENESIS

The IgAN pathogenesis is called the multi-hit hypothesis. Accumulation of IgA-containing immunocomplexes in glomeruli leads to overproduction of proliferation, chemokines, cytokines, extracellular matrix, and glomerular injury [15]. Sensitivity to IgAN is affected by environmental and genetic factors [16]. Experimental studies support that environmental factors may cause excessive aberrantly-glycosylated IgA production in mucosal-associated lymphoid tissue [17]. There are two separate isotypes (IgA1-IgA2) as IgA in serum and mucosa. IgA in serum is mostly found in monomeric form. In humans, the production of immunoglobulins is detected daily at approximately 70 mg / kg / day for IgA, 22 mg / kg / day for IgG and 7 mg / kg / day for IgM, respectively. Plasma IgA levels are lower than other immunoglobulins since they have short half-life [13]. Approximately 85% of total IgA is IgA1. This was consistent with the production of more IgA1 than plasma cells in this bone marrow. Polymeric IgA is more common in external secretions [18]. While IgA2 secreting cells are more dominant in the female reproductive system and the colon, IgA1 are more dominant in the lacrimal glands, salivary glands, respiratory system and upper gastrointestinal tract [19]. IgA1 and IgA2 are predominantly secretory IgA in mucosal secretions. Secretory IgA is the first defense of mucosal immunity [20]. To pass through the mucosal epithelium, the IgA is bound to the Polymeric Immunglobulin Receptor (pIgR) on the basoletal surface in the epithelium. The resulting dimeric IgA / pIgR complex is taken up into membrane vesicles and transferred to the apical cell surface. Dimeric IgA is then released in to mucosal secretions with a secretory component, the extracellular portion of the pIgR. Both components form secretory IgA [21]. IgA is anti-inflammatory antibody as a primer. The presence of secretory IgA on mucosal surfaces allows the inflammatory processes to be controlled. Secretory IgA prevents mucosal wall penetration of foreign antigens or pathogenic microorganisms and forms an antiseptic barrier [22]. As a result of genetic or acquired regulation abnormality in the mucosal immunity, B cells exposed to a large number of environmental antigens (bacteria, viruses, food proteins) synthesize an excessive amount of defective galactosylated polymeric IgA1 molecule. This altered galactosylation also increases the binding of polymeric IgAl to the kidney mesangial cells and induces a number of mediators such as cytokines, chemokines and growth factor. In patients with IgAN, polymeric IgA1 is increased, unlike the monomeric form that normally prevails in serum, and is more polymeric IgA1 in IgA that accumulates in the glomeruli. Poorly O-galactosylated IgA1 is an important observation in the IgAN pathogenesis that increased serum and glomerular accumulations are present. IgA1 has an extended hinge region of 18 amino acids between the first and second constant domains of the heavy chain. The "O" glycans in this region are linked to the serine and threonine residues of the chain. There are probably a total of 9 serine / treaon regions in each alpha chain that O-galactosylation can use. But O-galactosylation can only invade the region 3-6 at any time. O-galactosylation of the hinge region occurs through a group of enzymes. In this process, with N-acetylgalactosaminyl-transferase activity, the IgA1 hinge region begins by adding N-acetylgalactosamine to the serine and threonine residues via an oxygen atom. Next, a portion of galactose is added to the core 1 beta 1, 3 galactosyltransferase and N-acetylgalactosamine. Then sialic acid may be added a 2,3 sialyransferase with galactose moiety or α2,6 sialytransferase with N-acetylgalactosamine. N-acetylgalactosamine prevents sialylation with galactose. For this reason IgA1 is an important step in O-galactosylation [20,23,24].

There is evidence that genetic factors play an important role in influencing circulating composition of IgA1 O glycoforms in serum. Both familial and sporadic IgAN until the first degree relatives, poorly O galactosylated IgA1 level was found high. Studies have shown that galactose-deficient IgA1 levels are elevated in serum in IgAN patients and first-degree relatives. Galactose-deficient IgA1 level was found in 25% of blood relatives of IgA patients [16,25,26]. In one study, serum poorly O galactosylated IgA1 levels were associated with the noncoding region of C1GALT1. This gene is responsible for encoding C1GalT1 galactosyltransferase. Poorly O-galactosylated IgA1 levels in the circulation are affected by inherited and genetic variations in the C1GALT1 gene [27]. IgAN B cells, Toll-like Receptors (TLR), and B-Cell Activating Factor (BAFF) and a Proliferation Inducing Ligand (APRIL) play an important role in the pathogenesis. Exposure to environmental and diet antigens activates mucosal B cell maturation by directly and indirectly activating TLR of mucosal infections. Together with these, it inadvertently directs the secretion of B cells (polymeric IgA1) to systemic circulation with BAFF and APRIL signals. Poorly galactosylated IgA1 passes through the systemic circulation. Circulating serum polymeric, poorly galactosylated IgA1 levels were increased. O-glycan specific autoantibodies are produced. IgA1 immunocomplexes are formed in this way. Circulating immune complexes accumulate in the kidney as mesangial and renal damage occurs as a result of mesangial cell and complex activation [28].

Characteristic mesangial granular IgA and C3 accumulation in the in immunofluorescent stain suggests that the disease is caused by the accumulation of circulating immune complexes that lead to alternative complement activation. Systemic and renal alternative complement activation was documented in IgAN patients. It is believed that both the alternative pathway and the abnormal activation of the mannose-binding lectin pathway play a role in the IgAN pathogenesis. Glomerular inflammation should be augmented by the complement system. Alternative complement pathway activation in adult IgAN patients is defined in the plasma at 30-75%. Recent studies have shown that proteins associated with compleman factor H play a role in IgAN patients. The deletion polymorphism in the CFHR1 and CFHR3 genes is protective against IgAN. In the absence of C1q in glomeruli, C4d staining may indicate complement pathway activation. Approximately 40% of IgAN patients were stained with C4d in the glomeruli [29-31].

Gut-Associated Lymphoid Tissue (GALT) and intestinal microbiota plays a major role in the development of IgAN. The microbes on the mucosal surface are in close contact with the intestinal epithelium. These microbes influences the GALT modulation greatly by affecting the intestinal barrier against the pathogens and host immune system. The microbes effect the host innate and adaptive immune systems. An increased intestinal permeability was reported in patients with IgAN. Deterioration of the intestinal barrier may result in increased antigen uptake, mucosa-associated lymphoid tissue activation, and subclinical intestinal inflammation. Glycosylated polymeric IgA production is increased. Increased serum IgA results in mesangial deposition in the kidneys. Disruption of the intestinal barrier also contributes to uremic toxicity and systemic inflammation by facilitating the abnormal entry of bacterial lipopolysaccharide endotoxin into the circulation. There is significant correlation the degree of intestinal inflammation with serum IgA level, proteinuria and hematuria. Mucosal IgA production is induced by T cell independent or T cell dependent mechanisms. T cell in dependent production of IgA is stimulated by IL6, IL10, TGF beta, BAFF and APRIL. BAFF and APRIL lead to B cell activation. This is demonstrated by the overproduction of BAFF and APRIL, which play a critical role in IgA synthesis in transgenic mice. BAFF hyperexpression in transgenic mice is associated with polymeric IgA production and mesangial accumulation of IgA [32-37].

PATHOLOGY

IgAN is definetly diagnosed by renal biopsy. The dominant IgA accumulation should be shown in the renal biopsy. IgA accumulation is characterized by a + 1 intensity or more frequent +2 and more [38]. Among 1989 cases of IgAN compiled from 13 published biopsy series, 100% of cases had positivity for IgA, 45,8% had positivity for IgG and 53,7% for IgM, 92,6% had positively for C3, 11,2% had positively for C1q [39]. IgAN is defined as the immunohistology by the presence of immune accumulations of dominant or co-dominant IgA in glomeruli. Patients with lupus nephritis, IgA predominant postinfectious glomerulonephritis, and pure membrane distribution of IgA deposits (a rare phenomenon) are outside this definition. Histological changes are seen in a wide range IgAN renal biopsy. IgA deposits are most commonly detected only in the mesangium but additional capillary wall deposits are found in up to one-third of patients. Capillary wall IgA deposits are in a subendothelial location; subepithelial deposits are rare. Minimal histological changes can be mild proliferation or normal. Focal or diffuse mesangial proliferation is frequent in renal biopsies. This is often accompanied by an increased mesangial matrix. Endocapillary proliferation is detected in one third of the renal biopsies. In renal biopsies, ectsracellular proliferation and crescent are defined. Normal apperance or atrophy can be detected in renal tubules. In addition, interstitial fibrosis can develop. A new grading system called IgAN's Oxford Classification And MEST scoring system tries to score changes in different anatomical segments, including Mesangium hypercellularities (M), Endocapillary superselectivity (E), Segmental glomerulosclerosis (S) and Atrophy / interstitial fibrosis (T) [38,40,41] (Table 1).

CLINIC

IgAN affects mostly young adults. It is also seen in children and elderly people. IgAN can develop as a primer or as a secondary. Secondary causes of IgAN were given in table 2 [39]. The clinical spectrum is characterized by asymptomatic hematuria and proteinuria, with rapid deterioration of renal function. Hematuria of IgAN is the most common clinical presentation. Hematuria and clinical course are seen after a few days usually upper respiratory tract infections or, less frequently, gastrointestinal and urinary infections. Persistent microscopic hematuria is not IgAN specific. However, half of the renal biopsies performed in the microscopic haematuria were detected as IgAN. In IgAN patients, 70-100% of microscopic hematuria is seen (especially in children and young adults). The hematuria is glomerular origin which is shown by demonstration of dysmorphic red cells in the urine sediment. Glomerular hemorrhage is caused by wall damage of glomerular capillaries continuing with IgA immun complex accumulation. This event is the result of glomerular inflammation [42].

IgAN may cause asymptomatic proteinuria, proteinuria with hematuria or nephrotic proteinuria in patients. In IgAN patients, proteinuria is usually mild to moderate proteinuria. IgAN with nephrotic proteinuria is not common [43,44]. Nephrotic proteinuria indicates that it will be more severe histology and nephropathy. The frequency of IgAN nephrotic proteinuria is between 4.4-22.8%

[5,6,8,43,45].

Acute renal failure is a rare complication of IgAN. Recently, there have been few studies on acute renal failure in IgAN patients. The relationship between acute renal failure and macroscopic hematuria is widely known in IgAN patients. Acute tubuler necrosis is seen in IgAN patients which is commonly accompanied by macroscopic hematuria. It also occurs a few days after upper respiratory tract infection. Intratubular erythrocytic casts lead to tubular damage in the kidneys. Hemoglobin released from intratubular erythrocytic casts is probably nephrotoxic [46]. The severity of acute tubular necrosis ranges from an increase in transient mild serum creatinine to oliguric renal insufficiency. There are several mechanisms leading to acute renal failure in IgAN. These include crescentic IgAN, acute tubuler necrosis associated with microhematuria, tubuler occlusion by red blood cells, acute tubular necrosis unrelated to microhematuria, and acute interstitial nephritis (possibly induced by drugs) [47]. In IgAN patients, elderly individual, malignant hypertension and proteinuria is at risk for acute renal failure. In studies comparing young people and the elderly, acute renal failure was found to be significantly higher in older people (52.9%) than in young people (12.2%). In addition, hypertension (88.2%) and nephrotic proteinuria (70.6%) were higher in the elderly than young people (hypertension 30.5% and nephrotic proteinuria 26.8%) [48]. In the study conducted, the incidence of acute renal failure was 6.7% in IgAN patients (1023 in total between 15-65 years). Also, in patients >65 years of age (a total of 108 patients) was found 27.6% rate for acute renal failure [49]. The pathological spectrum of acute renal failure is quite extensive. These include a significantly higher proportion of glomeruli with cellular crescent, fibrocellular crescent, interstitial cell infiltration, global sclerosis, segmental sclerosis, tubular atrophy, and interstitial fibrosis [44]. Histological findings in macroscopic hematuria-associated acute renal failure are acute tubular injury/necrosis and intraluminal obstruction by erythrocytes or hemoglobin casts [50]. Acute renal failure in IgAN was found between 2.6% and 9.5% [49,51,52]. In studies performed with IgAN, the rate of chronic renal failure was found to be 12,9% to 18,3% [49,52].

Table 1: MEST scoring system

Definition	Score	Histologycal variable
More than four mesangial cells in any mesangial area of a glomerulus	Mo	Mo < 50% of glomeruli showing mesangial hypercellularity (Mesangial hypercellularity)
	M1	M1 > 50% of glomeruli showing mesangial hypercellularity (Mesangial hypercellularity)
Hypercellularity due to an increased number of cells within glomerular capillary lumina	E0	no endocapillary hypercellularity (Endocapillary hypercellularity)
	E1	any glomeruli showing endocapillary hypercellularity (Endocapillary hypercellularity)
Adhesion or sclerosis (obliteration of capillary lumina by matrix) in part but not the whole glomerular tuft	S0	no segmental glomerulosclerosis
	S1	present in any glomeruli (segmental glomerulosclerosis)
Estimated percentage of cortical area showing tubular atrophy or interstitial fibrosis, whichever is greater	T0	0-25% of cortical area (Tubular atrophy/ interstitial fibrosis)
	T1	26-50% of cortical area (Tubular atrophy/ interstitial fibrosis)
	T2	>50% of cortical area (Tubular atrophy/ interstitial fibrosis)
Percentage of glomeruli with cellular or fibrocellular crescents	C0	no Cellular or fibrocellular crescents
	C1	0-25% of glomeruli (Cellular or fibrocellular crescents)
	C2	≥25% of glomeruli (Cellular or fibrocellular crescents)

M: Mesangial hypercellularity; C: Crescents; E: Endocapillary hypercellularity; S: Segmental glomerulosclerosis; T: Tubular atrophy/ interstitial fibrosis.

Table 2: Secondary IgAN

Hepatobiliary diseases	Cirrhosis secondary to Alcoholic liver disease Viral hepatitis Toxic liver disease Biliary cirrhosis/biliary atresia Cystic fibrosis Noncirrhotic portal hypertension Interleukin-2 therapy for hepatocellular carcinoma
Gastrointestinal disease	Coliac disease Crohn's disease Ulcerative colitis
Rheumatologyc disease	Ankylosing spondylitis Rheumatoid arthritis Psoriatic arthritis Reiter's syndrome Behçet's disease
Infectious disease	Human immunodeficiency virus Yersinia enterocolitica Campylobacter jejuni Clostridium difficile Mycoplasma pneumonia Tuberculosis Brusellosis Leprosy
Neoplatic and myeloproliferative diseases	Renal cell carcinoma Non-hodgkin's lymphomas Mycosis fungoides/Sezary syndrome Various carcinomas including squamous cell, bronchial small cell, and adenocarcinomas Mixed cryoglobulinemia Polycytemi,a vrea
Ophthalmologyc disease	Scleritis Uveitis with retinal vasculitis
Dermatologyc disease	Dermatitis herpetiformis Psoriasis
Miscellaneous pulmonary/systemic disease	Sarcoidosis Silicosis Bronchiolitis obliterans

The frequency of hypertension in IgAN patients was found to be 3.4-74%. Hypertension often increases with age and is accompanied by renal insufficiency and proteinuria [49,51-53]. Acute and chronic renal insufficiency rates were found to increase over 65 years [49]. The frequency of asymptomatic urinary anomalies in IgAN was found to be 23.1-67.2% [5,6,49,54]. The frequency of nephritic syndrome was found to be 3.1-17.2% in studies done with IgAN [4,5,49]. 65.1% of the patients had prodramal infection and most of them were described as upper respiratory tract infection [54].

PROGNOSIS

Approximately 30-50% of IgA N patients develop ESRD and renal replacement therapy dialysis or transplantation is required [55,56]. Many factors influence the prognosis of IgAN. There is an important relationship between proteinuria and renal prognosis in IgAN patients. Proteinuria under 1gr/ day is good for renal prognosis. Nephrotic proteinuria is a poor prognostic indicator in IgAN patients. The study found that the incidence of dialysis and death was higher in patients with proteinuria of ≥3 gr / day. Proteinuria > 1 gr/ day indicates poor prognosis [43,45,57]. There is a low risk for progressive renal disease in patients with recurrent

hematuria without proteinuria, compared with patients' hematuria with the poteinuria [58]. Blood pressure heigh (> 140/ 90mmHg) is a poor prognostic indicator. In one study, cumulative 10-year and 20-year dialysis and mortality rates were found as 4% and 5% in patients without hypertension respectively, 1% and 19% in patients with controlled hypertension, respectively, and 19% and 42%, in patients with uncontrolled hypertension respectively [57]. In another study, renal function test results were better detected in persistent hematuria in patients with minimal or negative hematuria. 10.6% in cases with minimal or negative hematuria, and 30.4% in cases with peristent hematuria have developed ESRD. Decrease in renal function and decrease in rate of annual glomerular filtration were more frequent in persistant hematuria [59].

In the study of the relationship between the complement and prognosis, increased C4 and decreased C3 levels were associated with poor renal prognosis [60]. Mesangial C4d accumulation is associated with impaired renal function and is also a poor prognostic indicator [61]. In addition, hyperuricemia and moderate to severe mesangial c3 accumulation were identified as an independent risk factor for IgAN progression [62].

In the study on Vitamin D, the presence of vitamin D deficiency in the beginning has been associated with poor renal function, proteinuria, more severe pathologic findings and increased renal progressionin IgAN patients [63]. Smoking, obesity and hyperuricemia are also poor predictors of cognitive function. It affects renal prognosis in pathological findings. In a multi-centered study, M, S, T lesions are associated with an independent indicator of loss of glomerular filtration rate and low renal survival. M and T lesions show poor renal survival. There was no relationship between renal function and renal survival with endocapillary and extracapillary proliferase. Mesangial hypersellility, endocapillary hypersellularity, segmental sclerosis and tubuler atrophy / tubuler fibrosis show poor prognosis. The presence of renal biopsy crescent shows poor prognosis. Capillary wall IgA accumulation is associated with increased risk, mesangial and endocapillary hypersellularity, increased frequency of crescent and advanced chronic renal failure [64-66].

TREATMENT

KDIGO is recommended to provide target blood pressure. If proteinuria> 0.5gr / day, Angiotensinconverting Enzyme (ACE) Inhibitors or Angiotensin Receptor Blockers (ARB) treatment is recommended. Target blood pressure recommendations are suggested as if the amount of proteinuria is <1gr / day, the blood pressure <130 / 80mmHg and If the amount of proteinuria is> 1gr / day, blood pressure <125 / 75mmHg. Immunosuppressive therapy with GFR <30 ml / min is not recommended if there is no rapid renal function and crescentic glomerulonephritis [67].

Despite optimal conservative treatment, corticosteroid therapy is recommended for 6 months if the amount of persistent proteinuria is> 1gr / day for 3-6 months [67,68]. Steroid treatment regimens are suggested as 1gr methylprednisolone for 3 days in the first, third and fifth months, On other days oral 0.5 mg / kg / day methylprednisolone or for the first two months 0.8-1 mg / kg / day methylprednisolone and then 6 months by reducing dose [69]. In a study of 86 IgAN patients (GFR > 70 ml / min, basal serum creatinine <1.5 mg / dl and proteinuria 1-3.5 gr / day for these patients), 43 patients received only supportive care and 43 patients received supportive care +methylprednisolone. As a result of this study, it was better in the 10-year renal survival in methylprednisolone group (97% in the methylprednisolone group and 53% in the control group). The proteinuria response was 30% in the control group and 72% in the methylprednisolone group. Of the total 14 patients with end-stage renal disease, 13 were under supportive care, one patient was in the methylprednisolone group [70]. In another study of 262 patients, the protened amount of these patients, compared with steroids and placebo, was over 1grs/ day. Proteinuria reduction in the steroid group was significantly better in the first 12 months. Side effects were 14.7% in the steroid group and 3.2% in the control group [71].

Mycophenolate mofetil (MMF) is seen to be effective in studies. However, KDIGO does not recommend the use of MMF [67]. In a study involving 40 patients, 20 patients received MMF or others placebo. In this study, in the MMF group, ESRD is 10% [2], in the control group, 45% [9] developed and dialysis was necessary. The 6-year renal survival was 90% in the MMF group and 55% in the control group [72]. As a result of a metaanalysis study, MMF monotherapy was found to be more effective and to have a significantly higher remission rate than placebo and steroid monotherapy. However, the side effect frequency of MMF monotherapy is more abused. When steroid therapy combined with MMF and steroid treatment combined with cyclophosphamide compared, in the MMF group, the remission rates were significantly higher [73]. In another study, 42 patients received steroid therapy combined with MMF and 42 patients received combination of cyclophosphamide and steroids. While complete remission was 38.1% and partial remission was 47.6% in MMF group, complete remission was 21.4% and partial remission was 40.4% in cyclophosphamide group. Side effects were 4.7% in the MMF group while 26.2% in the cyclophosphamide group [74]. In another study, steroid combined with MMF and isolated steroid treatment were compared. After 12 months, complete remission was 48% and total remission was 82% in MMF group, complete remission was 53% and total remission was 85% in steroid group. There was no difference between the two groups in terms of side effects [75].

Hydroxychloroquine is an antimalarial drug that reduces TLR and INF gamma, IL-6 and TNF alpha, which play a role in the pathogenesis of IgAN. In one study, losartan and hydroxychloroquine were started in a group of patients with persistent proteinuria IgA and the other group were given only losartan. In group one, complete and partial remission was 42.9% while in group two they were 14.3% [76]. In a study comparing low-dose steroids +leflunomid with high-dose steroids, the ESRD development rate was 7.5% in the leflunomide group and 11.1% in the steroid group. 50% increase in serum creatinine, 20% in the steroid group, 10% in the leflunomide group and in the steroid group total remission rate 68.9% and 67.5% in the leflunomide group [77]. As a result of a meta-analysis, calcitriol treatment showed reduced proteinuria in nonnephrotic proteinuria in IgAN patients [78].

In a meta-analysis, calcineurin inhibitor and steroid therapy have been found to be effective and safe in IgAN patients. Compared with patients who received steroid alone, there was an increase in remission in patients receiving calcineurin + steroids. There was no difference between the two groups in terms of partial remission. Side effects were less frequent in the calcineurin group [68].

The KDIGO suggested that tonsillectomy should not be performed to treat IgAN routinely [67]. But, some recent meta-analyzes results have been shown that tonsillectomy induces not only adjuvant treatment but also clinical remission independently. In addition, tonsillectomy has been shown to reduce the rate of ESRD [79,80].

Diffuse crescent formation occurs under 5% of all IgAN patients. And this leads to rapid progressive glomerulonephritis. If there is rapidly worsening renal function in KDIGO IgAN, and if crescentic glomerulonephritis, corticosteroids and cyclophosphamide are recommended [67]. Crescentic IgAN is progressing more than 50% ESRD in a short time. Patients with crescentic IgAN and high serum creatinine levels were given cyclophosphamide and 3 days 1 gr then 1 mg / kg / day methylprednisolone 6 months. In these patients, at the end of 6th month ESRD was % 72. At the end of 6th month ESRD was % 77,7 furthermore, partial remission was 22.2% at 6 months and 11.1% at 12 months and none of these patients had a complete remission [81]. A child with rapid progressive IgAN has been successfully treated with plasma exchange in addition to immunosuppressive treatment. In a study conducted in severely crescent-shaped IgAN patients, A total of 12 patients underwent plasma exchange (mean 7 sessions) and were shown to be effective in increasing renal healing [82,83].

ω-3 polyunsaturated fattyacids is abundant in fish oil shows an anti-inflammatory effect via suppressing IL6-induced abnormal IgA production and IgA-containing immunocomplex accumulation in the mesangial region [84,85]. In IgAN patients, anti-gliadin antibodies are detected in the circulation. In a study of mice with gluten-free diet, there was a decrease in hematuria, proteinuria, IgA immunocomplex accumulation and antigliadin but there was no difference in renal function decline at 4 years follow-up [86]. Blisibimod and atacicept are currently being evaluated in separate phase II studies in IgAN. Both agents target the BAFF and APRIL signaling pathways. Blisibimod is a selective peptibody antagonist of BAFF [87].

As a result, IgAN usually presents mildly or moderately proteinuria in patients. Nephrotic proteinuria and acute renal failure are rarely seen in IgAN patients. Nephrotic proteinuria shows poor prognosis. In addition to conservative treatment, dietary management for IgAN patients are recommended. Gluten-free diet is advisable for patients having antigliadin in their circulation. Immunosuppressive therapy is used in the treatment of IgAN. Combination immunosuppressive therapy is recommended in the presence of crescent. It seems that the optimal treatment of IgAN still needs to be investigated. Especially the treatment of pathogenesis seems to gain importance.

REFERENCES

1. Kim JK, Kim JH, Lee SC, Kang EW, Chang TI, Moon SJ, et al. Clinical features and outcomes of IgA nephropathy with nephrotic syndrome. Clin J Am Soc Nephrol. 2012; 7: 427-436. https://goo.gl/NZ4DUx
2. Donadio JV, Bergstralh EJ, Grande JP, Rademcher DM. Proteinuria patterns and their association with subsequent end-stage renal disease in IgA nephropathy. Nephrol Dial Transplant 2002; 17: 1197-1203. https://goo.gl/cHHG2Q
3. Moriyama T, Tanaka K, Iwasaki C, et al. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. PLoS One. 2014; 9: 91756. https://goo.gl/mLwbXJ
4. Rivera F, Lopez-Gomez JM, Perez-Garcia R. Frequency of renal pathology in Spain 1994-1999. Nephrol Dial Transplant 2002; 17: 1594-1602. https://goo.gl/mKNo5T
5. Rychlík I, Jancová E, Tesar V, Kolsky A, Lácha J, Stejskal J, et al. The Czech registry of renal biopsies. Occurrence of renal diseases in the years 1994-2000. Nephrol Dial Transplant. 2004; 19: 3040-3049. https://goo.gl/c2jybt
6. Ozturk S, Sumnu A, Seyahi N, Gullulu M, Sipahioglu M, Artan S, et al. Demographic and clinical characteristics of primary glomerular diseases in Turkey. Int Urol Nephrol. 2014; 46: 2347-2355. https://goo.gl/aSmywk
7. Li LS, Liu ZH. Epidemiologic data of renal diseases from a single unit in China: analysis based on 13,519 renal biopsies. Kidney Int. 2004; 66: 920-923. https://goo.gl/xkgYvT
8. Jiang M, Xiao Z, Rong L, Xu Y, Chen L, Mo Y, et al. Twenty-eight-year review of childhood renal diseases from renal biopsy data: A single centre in China. Nephrology (Carlton). 2016; 21: 1003-1009. https://goo.gl/5mmCo8
9. Sugiyama H, Yokoyama H, Sato H, Saito T, Kohda Y, Nishi S, et al. Japan Renal Biopsy Registry: the first nation wide, web-based, and prospective registry system of renal biopsies in Japan. Clin Exp Nephrol. 2011; 15: 493-503. https://goo.gl/JbQX7m
10. Shin HS, Cho DH, Kang SK, Kim HJ, Kim SY, Yang JW, et al. Patterns of renal disease in South Korea: a 20-year review of a single-center renal biopsy data base. Ren Fail. 2017; 39: 540-546. https://goo.gl/BDTwxM
11. Malafronte P1, Mastroianni KG, Betônico GN, Romão JE Jr, Alves MA, Carvalho MF, et al. Paulistaregistry of glomerulonephritis: 5-year datareport. Nephrol Dial Transplant. 2006; 21: 3098-3105. https://goo.gl/MZ4Wma
12. Nair R, Walker PD. Is IgA nephropathy the commonest primary glomerulopathy among young adults in the USA? Kidney Int. 2006; 69: 1455-1458. https://goo.gl/Ffp6b9
13. Mestecky J, Raska M, Julian BA, Gharavi AG, Renfrow MB, Moldoveanu Z, et al. IgA nephropathy: molecular mechanisms of the disease. Annu Rev Pathol. 2013; 8: 217-240. https://goo.gl/291cHH
14. Coppo R, Troyanov S, Bellur S, Cattran D, Cook HT, Feehally J, et al. Validation of the Oxford classification of IgA nephropathy in cohorts with different presentations and treatments. Kidney Int. 2014; 86: 828-836. https://goo.gl/vUjLrC
15. Suzuki H, Kiryluk K, Novak J, Moldoveanu Z, Herr AB, Renfrow MB, et al. The pathophysiology of IgA nephropathy. J Am Soc Nephrol. 2011; 22: 1795-1803. https://goo.gl/WRCLZa
16. Kiryluk K, Moldoveanu Z, Sanders JT, Eison TM, Suzuki H, Julian BA, et al. Aberrant glycosylation of IgA1 is inherited in bothpediatric IgA nephropathyand Henoch-Schonlein purpura nephritis. Kidney Int. 2011; 80: 79-87. https://goo.gl/WoxY6p
17. Schiemann B, Gommerman JL, Vora K, Cachero TG, Shulga-Morskaya S, Dobles M, et al. An essential role for BAFF in the normal development of B cells through a BCMA-independent pathway. Science. 2001; 293: 2111-2114. https://goo.gl/9D7A8M
18. Woof JM, Mestecky J. Mucosal immunoglobulins. Immunol Rev. 2005; 206: 64-82. https://goo.gl/D62Hvp
19. Brandtzaeg P, Johansen FE. Mucosal B cells: phenotypic characteristics, transcriptional regulation, and homing properties. Immunol Rev. 2005; 206: 32-63. https://goo.gl/74UuLb
20. Woof JM, Russell MW. Structure and function relationships in IgA. Mucosal Immunol. 2011; 4: 590-597. https://goo.gl/76V8hd
21. Robert T, Berthelot L, Cambier A, Rondeau E, Monteiro RC. Molecular insights into the pathogenesis of IgA nephropathy. Trends Mol Med. 2015; 21: 762-775. https://goo.gl/xhMH7X
22. Mathias A, Pais B, Favre L, Benyacoub J, Corth B. Role of secretory IgA in the mucosal sensing of commensal bacteria. Gut Microbes. 2014; 5: 688-695. https://goo.gl/pdX9Kc
23. Suzuki H, Moldoveanu Z, Hall S, Brown R, Vu HL, Novak L, et al. IgA1-secreting cell lines from patients with IgA nephropathy produce aberrantly glycosylated IgA1. J Clin Invest. 2008; 118: 629-639. https://goo.gl/PwvAao
24. Raska M, Moldoveanu Z, Suzuki H, Brown R, Kulhavy R, Andrasi J, et al. Identification and characterization of CMP-NeuAc: GalNAc-IgA1 α 2,6-sialyltransferase in IgA1-producing cells. J Mol Biol. 2007; 369: 69-78. https://goo.gl/DuyYnd
25. Hastings MC, Moldoveanu Z, Julian BA, Novak J, Sanders JT, McGlothan KR, et al. Galactose-deficient IgA1 in African Americans with IgA nephropathy: serum levels and heritability. Clin J Am Soc Nephrol. 2010; 5: 2069-2074. https://goo.gl/Nch6FK
26. Gharavi AG, Moldoveanu Z, Wyatt RJ, Barker CV, Wood ford SY, Lifton RP, et al. Aberrant IgA1 glycosylation isinherited in familial and sporadic IgA nephropathy. J Am Soc Nephrol. 2008; 19: 1008-1014. https://goo.gl/xR2AKL

27. Gale DP, Molyneux K, Wimbury D, Higgins P, Levine AP, Caplin B, et al. Galactosylation of IgA1 is associated with common variation in C1GALT1. J Am Soc Nephrol. 2017; 28: 2158-2166. https://goo.gl/tHLBr2

28. Yeo SC, Liew A, Barratt J. Emerging therapies in immunoglobulin a nephropathy. Nephrology (Carlton). 2015; 20: 788-800. https://goo.gl/r44vTw

29. Magistroni R, D'Agati VD, Appel GB, Kiryluk K. New developments in the genetics, pathogenesis, and therapy of IgA nephropathy. Kidney Int. 2015; 88: 974-989. https://goo.gl/px86NY

30. Zhu L, Zhai YL, Wang FM, Hou P, Lv JC, Xu DM, et al. Variants in complement factor H and complement factor H-related protein genes, CFHR3 and CFHR1, affect complement activation in IgA nephropathy. J Am Soc Nephrol. 2015; 26: 1195-1204. https://goo.gl/BQkPEQ

31. Medjeral Thomas NR, Lomax Browne HJ, Beckwith H, Willicombe M, McLean AG, Brookes P, et al. Circulating complement factor H related proteins 1 and 5 correlate with disease activity in IgA nephropathy. Kidney Int. 2017. https://goo.gl/GJXgbB

32. Rostoker G, Wirquin V, Terzidis H, Petit PM, Chaumette MT, Delchier JC, et al. Mucosal immunity in primary glomerulonephritis. III. Study of intestinal permeability. Nephron. 1993; 63: 286-290. https://goo.gl/rSp2gj

33. Coppo R. The intestina-renal connection in IgA nephropathy. Nephrol Dial Transplant. 2014. 30: 360-6. https://goo.gl/b7Adn8

34. Evenepoel P, Poesen R, Meijers B. The gut-kidney axis. Pediatr Nephrol. 2016. https://goo.gl/1oQWnZ

35. Kiryluk K, Novak J. The genetics and immunobiology of IgA nephropathy. J Clin Invest. 2014; 124: 2325-2332. https://goo.gl/hwfmhW

36. Woof JM, Kerr MA. The function of immunoglobulin A in imunity. J Pathol. 2006; 208: 270-282. https://goo.gl/dMD6C9

37. Coppo R. The gut-kidney axis in IgA nephropathy: role of microbiota and diet on genetic predisposition. Pediatr Nephrol. 2017. https://goo.gl/qBehf8

38. Roberts IS, Cook HT, Troyanov S, Alpers CE, Amore A, Barratt J, et al. The Oxford classification of IgA nephropathy: pathology definitions, correlations, and reproducibility. Kidney Int. 2009; 76: 546-556. https://goo.gl/54kQgQ

39. Haas M. IgA Nephropathy and Henoch-Schonlein Purpura Nephritis. In: Jennette, JCDAVD, Olson JL, Silva FG, editors. Heptinstall's Pathology of the Kidney. 7. Philadelphia: Lippincott Williams & Wilkins. 2007.

40. Roberts IS. Pathology of IgA nephropathy. Nature reviews Nephrology. 2014; 10: 445-454. https://goo.gl/HzMmhH

41. Jennette JC. The immunohistology of IgA nephropathy. American journal of kidney diseases: the official journal of the National Kidney Foundation. 1988; 12: 348-52.

42. Coppo R, Fervenza FC. Persistent Microscopic Hematuria as a Risk Factor for Progression of IgA Nephropathy: New Floodlight on a Nearly Forgotten Biomarker. J Am Soc Nephrol. 2017. https://goo.gl/rGeSUH

43. Kim JK, Kim JH, Lee SC, Kang EW, Chang TI, Moon SJ, et al. Clinical features and outcomes of IgA nephropathy with nephrotic syndrome. Clin J Am Soc Nephrol. 2012; 7: 427-436. https://goo.gl/dxbdN5

44. Sevillano AM, Gutiérrez E, Yuste C, Cavero T, Mérida E, Rodríguez P, et al. Remission of Hematuria Improves Renal Survival in IgA Nephropathy. J Am Soc Nephrol. 2017. https://goo.gl/C4k33H

45. Moriyama T, Nakayama K, Iwasaki C, Ochi A, Tsuruta Y, Itabashi M, et al. Severity of nephrotic IgA nephropathy according to the Oxford classification. Int Urol Nephrol. 2012; 44:1177-1184. https://goo.gl/iLh1cq

46. Gutiérrez E, González E, Hernández E, Morales E, Martínez MA, Usera G, ey al. Factors that determine an incomplete recovery of renal function in macrohematuria-induced acute renal failure of IgA nephropathy. Clin J Am Soc Nephrol. 2007; 2: 51-57. https://goo.gl/sEZ5oJ

47. Wen YK, Chen ML. The spectrum of acute renal failure in IgA nephropathy. Ren Failure. 2010; 32: 428-433. https://goo.gl/F3ZpPJ

48. Wen YK, Chen ML. Differences in new-onset IgA nephropathy between young adults and the elderly. Ren Failure, 2010; 32: 3: 343-348. https://goo.gl/5cqo5M

49. Rivera F, López GJM, Pérez GR. Clinicopathologic correlations of renal pathology in Spain. Kidney Int. 2004; 66: 898-904. https://goo.gl/ip52Tz

50. Le W, Liang S, Chen H, Wang S, Zhang W, Wang X, et al. Long-term outcome of IgA nephropathy patients with recurrent macroscopic hematuria. Am J Nephrol. 2014; 40: 43-50. https://goo.gl/SVLx1D

51. Zhang L, Li J, Yang S, Huang N, Zhou Q, Yang Q, et al. Clinicopathological features and risk factors analysis of IgA nephropathy associated with acute kidney injury. Ren Fail. 2016; 38: 799-805. https://goo.gl/CfcsD1

52. Das U, Dakshinamurty KV, Prayaga A, Uppin M. Spectrum of IgA nephropathy in a single center. Saudi J Kidney Dis Transpl. 2015; 26: 1057-1063. https://goo.gl/q9oV5u

53. Ibels LS, Gryory AZ. IgA nephropathy: Analysis of the natural IgA nephropathy in african- American children. Pediatr Nephrol. 1997; 11: 435.

54. Tan M, Li W, Zou G, Zhang C, Fang J. Clinicopathological features and outcomes of IgA nephropathy with hematuria and/or minimal proteinuria. Kidney Blood Press Res. 2015; 40: 200-206. https://goo.gl/zX33EA

55. Moriyama T, Tanaka K, Iwasaki C, Oshima Y, Ochi A, Kataoka H, et al. Prognosis in IgA nephropathy: 30-year analysis of 1,012 patients at a single center in Japan. PLoS One. 2014; 9: 91756. https://goo.gl/RVW42Y

56. Wyatt RJ, Julian BA. IgA nephropathy. N Engl J Med. 2013; 368: 2402-2414. https://goo.gl/rCrBzH

57. Berthoux F, Mohey H, Laurent B, Mariat C, Afiani A, Thibaudin L. Predicting the risk for dialysis or death in IgA nephropathy. J Am Soc Nephrol. 2011; 22: 752-61. https://goo.gl/zf7JhP

58. Haas M. Histologic sub classification of IgA nephropathy: a clinicopathologic study of 244 cases. Am J Kidney Dis. 1997; 29: 829-842. https://goo.gl/ybKg3C

59. Sevillano AM, Gutiérrez E, Yuste C, Cavero T, Mérida E, Rodríguez P, et al. Remission of Hematuria Improves Renal Survival in IgA Nephropathy. J Am Soc Nephrol. 2017. https://goo.gl/sebCGP

60. Pan M, Zhang J, Li Z, Jin L, Zheng Y, Zhou Z, et al. Increased C4 and decreased C3 levels are associated with a poor prognosis in patients with immunoglobulin A nephropathy: a retrospective study. BMC Nephrol. 2017; 18: 231. https://goo.gl/2XW7fq

61. Fabiano RCG, de Almeda Araujo S, Bambirra EA, Oliveira EA, Simoes E Silva AC, Pinheiro SVB. Mesangial C4d deposition may predict progression of kidney disease in pediatric patients with IgA nephropathy. Pediatr Nephrol. 2017; 32: 1211-1220. https://goo.gl/pGgHb6

62. Caliskan Y, Ozluk Y, Celik D, Oztop N, Aksoy A, Ucar AS, et al. The clinical significance of uric acidand complement activation in the progression of Iga nephropathy. Kidney Blood Press Res. 2016; 41: 148-157. https://goo.gl/o1F1wY

63. Li XH, Huang XP, Pan L, Wang CY, Qin J, Nong FW, et al. Vitamin D deficiency may predict a poorer outcome of IgA nephropathy. BMC Nephrol. 2016; 17: 164. https://goo.gl/pPjCsh

64. Bellur SS, Troyanov S, Cook HT, Roberts IS. Immunostaining findings in IgA nephropathy: correlation with histology and clinical outcome in the Oxford classification patient cohort. Nephrol Dial Transplant. 2011; 26: 2533-2536. https://goo.gl/bEK5zh

65. Andreoli SP, Yum MN, Bergstein JM. Significance of glomerular basement membrane deposition of IgA. Am J Nephrol. 1986; 6: 28-33. https://goo.gl/mghYBJ

66. Cattran DC, Coppo R, Cook HT, Feehally J, Roberts IS, Troyanov S, et al. The Oxford classification of IgA nephropathy: rationale, clinicopathological correlations, and classification. Working Group of the International IgA Nephropathy Network and the Renal Pathology Society. Kidney Int. 2009; 76: 534-545. https://goo.gl/jHjczc

67. Kidney disease ımproving global outcomes glomerulonephritis work group: KDIGO clinical practice guideline for glomerulonephritis. Kidney Int. 2012; 2: 139-274. https://goo.gl/gCF7RQ

68. Peng W, Tang Y, Jiang Z, Li Z, Mi X, Qin W. The effect of calcineurin inhibitors in the treatment of IgA nephropathy: A systematic review and meta-analysis (PRISMA). Medicine (Baltimore). 2016; 95: 4731. https://goo.gl/7PH9os

69. Coppo R. Corticosteroids in IgA Nephropathy: Lessons from Recent Studies. J Am Soc Nephrol. 2017; 28: 25-33. https://goo.gl/wBh65r

70. Pozzi C, Andrulli S, Del Vecchio L, Melis P, Fogazzi GB, Altieri P, Ponticelli C, Locatelli F. Corticosteroid effectiveness in IgA nephropathy: long-term results of a randomized, controlled trial. J Am Soc Nephrol. 2004; 15: 157-163. https://goo.gl/9MgmpN

71. Lv J, Zhang H, Wong MG, Jardine MJ, Hladunewich M, Jha V, et al. Effect of oral methylprednisolone on clinical outcomes in patients with ıga nephropathy: The TESTING randomized clinical trial. JAMA. 2017; 318: 432-442. https://goo.gl/tvEziX

72. Tang SC, Tang AW, Wong SS, Leung JC, Ho YW, Lai KN. Long-term study of mycophenolate mofetil treatment in IgA nephropathy. Kidney Int. 2010; 776: 543-549. https://goo.gl/cUiezC

73. Du B, Jia Y, Zhou W, Min X, Miao L, Cui W. Efficacy and safety of mycophenolate mofetil in patients with IgA nephropathy: an update meta-analysis. BMC Nephrol. 2017; 18: 45. https://goo.gl/xqT7Dt

74. Liu X, Dewei D, Sun S, Xu G, Liu H, He L, Zhang P. Treatment of severe IgA nephropathy: mycophenolate mofetil/prednisone compared to cyclophosphamide/prednisone. Int J Clin Pharmacol Ther. 2014; 52: 95-102. https://goo.gl/Xykgd4

75. Hou JH, Le WB, Chen N, Wang WM, Liu ZS, Liu D, et al. Mycophenolate mofetil combined with prednisone versus full-dose prednisone in ıga nephropathy with active proliferative lesions: a randomized controlled trial. Am J Kidney Dis. 2017; 69: 788-795. https://goo.gl/nBvBjv

76. Gao R, Wu W, Wen Y, Li X. Hydroxychloroquine alleviates persistent proteinuria in IgA nephropathy. Int Urol Nephrol. 2017; 49: 1233-1241. https://goo.gl/jBBjBp

77. Min L, Wang Q, Cao L, Zhou W, Yuan J, Zhang M, Che X et al. Comparison of combined leflunomide and low-dose corticosteroid therapy with full-dose corticosteroid monotherapy for progressive IgA nephropathy. Oncotarget. 2017; 8: 48375-48384. https://goo.gl/quNg7S

78. Deng J, Zheng X, Xie H, Chen L. Calcitriol in the treatment of IgA nephropathy with non-nephrotic range proteinuria: a meta-analysis of randomized controlled trials. Clin Nephrol. 2017; 87: 21-27. https://goo.gl/kWiU5F

79. Liu LL, Wang LN, Jiang Y, Yao L, Dong LP, Li ZL, et al. Tonsillectomy for IgA nephropathy: a meta-analysis. Am J Kidney Dis. 2015; 65: 80-7. https://goo.gl/AJgr2a

80. Duan J, Liu D, Duan G, Liu Z. Long-term efficacy of tonsillectomy as a treatment in patients with IgA nephropathy: a meta-analysis. Int Urol Nephrol. 2017; 49: 103-112. https://goo.gl/B3o9o9

81. Ramachandran R, Doddi P, Nandakrishna B, Nada R, Kumar V, Rathi M, et al. Combination of pulse cyclophosphamide and steroids in crescentic IgA nephropathy. Int Urol Nephrol. 2015; 47: 1917-1918. https://goo.gl/Z1p6ME

82. Fujinaga S, Ohtomo Y, Umino D, et al. Plasma exchange combined with immunosuppressive treatment in a child with rapidly progressive IgA nephropathy. Pediatr Nephrol 2007; 22: 899-902. https://goo.gl/Mc8ybj

83. Xie X, Lv J, Shi S, Zhu L, Liu L, Chen M, et al. Plasma exchange as an adjunctive therapy for crescentic ıga nephropathy. Am J Nephrol. 2016; 44: 141-149. https://goo.gl/Mc8ybj

84. Dong W, Sell JE, Pestka JJ. Quantitative assessment of mesangial immunoglobulin A (IgA) accumulation, elevated circulating IgA immune complexes, and hematuria during vomitoxin-induced IgA nephropathy. Fundam Appl Toxicol. 1991; 17: 197-207. https://goo.gl/zuLHxf

85. Pestka JJ, Zhou HR. Interleukin-6-deficient mice refractory to IgA dysregulation but not anorexia induction by vomitoxin (deoxynivalenol) ingestion. Food Chem Toxicol. 2000; 38: 565-575. https://goo.gl/fYWj4N

86. Coppo R, Amore A, Roccatello D. Dietary antigens and primary immunoglobulin a nephropathy. J Am Soc Nephrol. 1992; 2: 173-180. https://goo.gl/dCR8u8

87. Yeo SC, Cheung CK, Barratt J. New insights into the pathogenesis of IgA nephropathy. Pediatr Nephrol. 2017. https://goo.gl/aSfKHP