Unfavorable prognostic factors in Immunoglobulin A Nephropathy

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Abstract

Immunoglobulin A nephropathy (IgAN) is a clinicopathological entity characterized by diffuse glomerular mesangial deposition of IgA as the predominant immunoglobulin. Renal biopsy reveals a spectrum of changes in the glomerul, tubulointerstitium and blood vessels. 20-50% of all patients develope end-stage renal failure 20 years after onset of the disease.

The aim of this stady was to analized influence of clinicopathological and laboratory changes to prognosis of IgAN. The study included 60 patients with biopsy-proven IgAN without some other systemic diseases or purpura Henoch-Schőnlein. We analized influence of clinical features of the disease, laboratory and immunofluorescence/light microscopy findings on the prognosis of IgAN. The study was partly retrospective and partly prospective. At the moment of renal biopsy 63,16% of patients had normal renal function, 31,58% had stage I and 5,25% had stage II chronic renal failure. At the end of study 21,05% of investigated patients progressed to a worse stage of renal failure with regard to the initial stage.

In this study we found severe histopathological changes in the group with already impaired renal function and these changes correlated with laboratory findings, clinical features and prognosis of the disease. Normal renal function at the moment of renal biopsy provides smaller risk of further damage. Changes in the tubulointerstitium, mesangium, heavy proteinuria and hypertension influence to worse prognosis of disease. Crossing to the higher stage of renal failure was 1,24% per year and this requires long-term follow-up of patients with IgAN.

Key words: IgA nephropathy, renal biopsy, outcome

Introduction

Immunoglobulin A nephropathy (IgAN), immunoglobulin A glomerulonephritis (IgAGN) or Berger's disease is a special clinical/pathological entity which is characterized by the finding of immunofluorescent microscopy with predominant IgA deposits in mesangium of the glomerul.

Morphological characteristics of the nephrotic damages in IgAN, similarly to clinical manifestation of the disease, are of a different form and degree of attack on glomerul, tubule, interstitium and blood vessels. Clinical progress of the disease is in correlation with histopathological changes with existence of significant clinical/pathological correlation with disease prognosis (1,2). Clinical and histopathological indicators (present at the moment of diagnosis) of the unfavorable disease prognosis are: 1) older age, 2) male sex, 3) absence of episodes of macrohematuria, 4) lower intensity value of glomerular filtration (IGF), 5) heavier proteinuria (>1000mg/24h) or proteinuria of nephrotic rank, 6) arterial hypertension, 7) more pronounced histopathological changes, 8) intensive IgA and C3 immunofluorescent deposits in glomerul and capillary wall, commonly associated with IgG deposits and fibrinogen are also considered to be the markers of unfavorable prognosis, 9) as the independent factors of the unfavorable disease prognosis, one can account for diabetes mellitus, hypertriglyceridemia, hyperuricemia, period of disease duration, positive family history (3-8).

IgA nephropathy was firstly called benign recurrent hematuria, however, a long-term follow-up of the renal function has shown that IgAN represents a slow, progressive illness of a different result which includes a high incidence of progressive damage of renal function with development of terminal nephritic insufficiency in 20-50% of the diseased, 20 years after the beginning of the disease. The research has shown that the damage of the renal function is developed faster in patients with an initial impairment of renal function, in contrast to patients with relatively normal renal function at diagnosis (4,6). The most significant prognostic factors in IgA nephropathy are histopathological changes, so that the expressed mesangial proliferation, glomerulosclerosis, presence of crescent formations, arteriosclerosis, interstitial fibrosis represent histological markers of unfavorable prognosis. Glomerulosclerosis, focal-segmented and especially diffuse, influence renal function substantially more intensively than the proliferative changes. Tubulointerstitial infiltrate, especially T cellular (CD4+, CD8+) is in correlation with faster progression of the disease. Interstitial fibrosis, regardless of simultaneous presence or absence of glomerulosclerosis, is also a significant prognostic factor. This explains different rate of renal function damaging in patients with the same level of glomerular damage, but different considering the tubulointerstitial inflammatory infiltrate or sclerosis (1,3,6,9,10).

The aim of this study was to analyze the influence of clinical-pathological and laboratory changes on prognosis of IgAN. Considering the possibility of development and progression of chronic renal insufficiency, the justification of longer follow-up of the diseased was reviewed.

Patients and methods

Testing covered 60 patients, who had percutaneous renal biopsy at the Clinic of Nephrology and Clinical Immunology of Clinical Center Novi Sad. The tested patients had documentation which consisted of at least, the first control

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examination, i.e. they were followed-up for at least one month up to maximum 17 years. Criterion for inclusion into the study was the finding of IgA deposits, as a dominant immunoglobulin in the mesangium of glomerul, which was deduced by immunofluorescent microscopy, while the presence of Henoch-Schonlein purpura and some other systematic illness were excluded.

Immunohistological technique included the application of standard antiserums: anti-IgA, -IgG, -IgM, -C3, -C4, -C1q, -fibrin. The intensity of positive immunofluorescent finding was estimated semi-quantitatively with a precise localization of the deposits.

Results

Patients' age ranged from 14-56 years, with an average of 34.19 years. From the cohort of 60 patients, 70% were of male sex, while 30% of them were female.

At the moment of renal biopsy, i.e. the diagnostics of the disease, 36 patients (63.16%) had a normal renal function (creatinine < 107 μmol/l, clearance creatinine > 90 ml/min/m^2), 18 patients (31.58%) were in stadium I of renal insufficiency (creatinine < 133 μmol/l, clearance of creatinine 60-90 ml/min/m^2) and 3 patients (5.26%) were in stadium II of renal insufficiency (creatinine 133-440 μmol/L, clearance of creatinine 10-60 ml/min/m^2). Out of 36 patients, who at the moment of diagnostics had normal renal function, 31 patient (86,11%) preserved the renal function until the end of the follow-up, 5 patients (13,89%) moved to stadium I of renal insufficiency. 12 patients (66.67%) from the group of 18 patients with initial stadium I of renal insufficiency remained in this stadium, while 6 patients (33.33%) moved to stadium II. 2 patients (66.67%) from the group of 3 patients with initial stadium II remained in this stadium, while 1 patient (33.37%) moved to stadium III.

If we observe the total number of patients who moved from one stadium of renal insufficiency to another (0→I, I→II, II→III), their total number was 12 (21.05%) for the follow-up period of 17 years, i.e. 1.24% of patients annually moved to a higher stadium in relation to the initial renal function (Table 1).

Table 1. Relationship between beginning and end stage renal failure

Beginning stage	Number	Percent	Stage of renal function at the end of the study	Number	Percent
Normal function	36	63,16 %	**Normal function**	31	86,11%
			I stage of renal failure	5	13,89%
I stage of renal failure	18	31,58 %	**I stage of renal failure**	12	16,67%
			II stage of renal failure	6	33,33%
II stage of renal failure	3	5,26 %	**II stage of renal failure**	2	66,67%
			III stage of renal failure	1	33,37%
	57	100 %		57	100%

Within the group of patients with normal initial renal function, the existence of positive correlation was identified among: 1) changes in mesangium and increase of creatinine concentration, 2) changes in mesangium and appearance of microhematuria in clinical manifestation of the disease, 3) glomerulosclerosis and higher values of systolic blood pressure, 4) crescent formations and severity of proteinuria (Table 2).

Table 2. Positive correlation between pathological findings with clinical features and laboratory parameters in the group of patients with normal renal function at the beginning

Pathological findings	Laboratory findings	Degree of correlation
Mesangium	Creatinine concentraction increase	r=0,47
	Microhematuria	r=0,35
Glomerulosclerosis	Systolic blood presure	r=0,21
Crescent	Proteinuria	r=0,24

The conclusions of the testing of patients with the initial stadium I renal insufficiency are the following: 1) there is an easy connection of changes in mesangium with the increase of creatinine concentration, higher values of systolic and diastolic blood pressure, 2) there is a significant correlation of glomerulosclerosis with microhematuria and heavier proteinuria, 3) there is an easy correlation between the presence of crescent formations and heavier proteinuria, 4) the changes in interstitium are in correlation with systolic, diastolic blood pressure and heavier proteinuria, 5) the changes in tubule are in easy correlation with a heavier proteinuria and the appearance of microhematuria (Table 3).

Table 3. Positive correlation between pathological findings with clinical features and laboratory parameters in the group of patients with Ist stage of renal failure

Pathological findings	Laboratory findings	Degree of correlation
Mesangium	Creatinine concentration increase	r=0,30
	Systolic blood pressure	r=0,37
	Diastolic blood pressure	r=0,31
Glomerulosclerosis	Proteinuria	r=0,35
	Microhematuria	r=0,66
Crescent	Proteinuria	r=0,35
Intestitium	Proteinuria	r=0,71
	Systolic blood pressure	r=0,39
	Diastolic blood pressure	r=0,35
Tubulus	Proteinuria	r=0,33
	Microhematuria	r=0,25

Conclusions

In this study, we found severe histopathological changes in the group with already impaired renal function and these changes correlated with laboratory findings, clinical features and prognosis of disease. Normal renal function at the moment of renal biopsy provides smaller risk of further damage. Changes in the tubulointerstitium, mesangium, heavy proteinuria and hypertension influence the worsening of prognosis of the disease. Crossing to the higher stage of renal failure was 1.24% per year and this requires a long-term follow-up of patients with IgAN.

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