

Outcome results in children with IgA nephropathy: a single center experience

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Background: Immunoglobulin A nephropathy (IgAN) is the most common primary glomerulonephritis. Patients manifest variable clinical symptoms (eg, microhematuria) with preserved or progressive deterioration of renal function resulting in end-stage renal disease. The aim of this study was to evaluate patients from a single center to describe the clinical features, treatments, and follow-up results of those with the disease.

Methods: This is a retrospective data study of all children with IgAN. Patients who had a histopathologically proven diagnosis of IgAN and were followed up for at least 5 years were included in the study. Renal biopsy, graded as Hass classification, was performed on all patients. A total of 39 patients were included in the study.

Results: The mean follow-up time (\pm standard deviation) was 10.4 ± 3.51 (range 5–16) years. Twenty-nine patients (74.4%) were male and ten (25.6%) were female. Nineteen (48.7%) patients presented with recurrent macroscopic hematuria, ten (25.6%) with microscopic hematuria \pm proteinuria, six (15.4%) with nephritic syndrome, and four (10.3%) with nephrotic syndrome. All patients underwent a renal biopsy, which was graded according to the Hass classification. At the end of follow-up time, 18 (46.1%) patients were normal, 15 (38.5%) had minor urinary abnormalities, three (7.7%) had active renal disease, and three (7.7%) developed renal failure.

Conclusion: The results of the present study are better than those from most other series. The majority of children with IgAN in this study were admitted with recurrent macroscopic hematuria and found to have a good prognosis. We suggest that children with IgAN have a good prognosis in the first 5-year follow-up period.

Keywords: immunoglobulin A nephropathy, childhood, prognosis

Introduction

Immunoglobulin A (IgA) nephropathy (IgAN) is the most common form of glomerulonephritis in children and adolescents worldwide.^{1,2} The disease was described as a new clinical entity in 1968.² Kidney biopsy is essential for diagnoses that show a markedly expanded mesangium filled with IgA. The clinical presentation of IgAN varies across the spectrum of initial renal manifestations, ranging from microscopic hematuria to end-stage renal disease (ESRD). The prognosis was initially considered to be benign in children but long-term studies have shown that IgAN in children can follow the same progression as in adults.^{3,4} Furthermore, previous studies on this subject have shown that ESRD will occur in 6%–43% of patients with IgA nephropathy over a period of 10 years. Several factors affect the prognosis in patients with IgA nephropathy, such as elevated serum creatinine, heavy proteinuria, hypertension, and sex (with males more likely to have the disease).⁵

The aim of this study was to evaluate patients from a single center to describe the clinical features, treatments, and follow-up results of those with the disease.

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Patients and methods

This is a retrospective data study of all children with IgAN hospitalized at the Ege University, Faculty of Medicine, Department of Pediatric Nephrology, from January 1991 to December 2005. Patients who had a histopathologically proven diagnosis of IgAN and were followed up for at least 5 years were included in the study. All medical records were reviewed with emphasis on presenting symptoms, physical exam findings, laboratory data, therapies, and outcome. The local ethical committee approved all procedures in this study.

For each patient, the following information was completed from medical charts: patient age at time of biopsy, sex, serum creatinine (mg/dL), serum IgA levels; urinary protein excretion (g/24 hours or protein/creatinine ratio); presence or absence of gross and/or microscopic hematuria; and presence or absence of hypertension (blood pressure >95th percentile for age, gender, and height on repeated measurements). Hematuria was defined as a small amount (+) of hemoglobin on dipstick testing or greater than five red blood cells per high-power microscopic field in a centrifuged specimen.

Proteinuria was defined as a small amount of protein (+) on dipstick testing or proteinuria greater than 0.5 g/1.73 m²/day obtained from urine collected over 24 hours. The Schwartz formula was used to estimate creatinine clearance from the serum creatinine and height. Low creatinine clearance was defined as an estimated glomerular filtration rate (GFR) of <60 mL/min per 1.73 m² body surface area. These patients were classified according to the initial clinical presentation.⁶ This classification was used as follows: microscopic hematuria ± proteinuria; macroscopic hematuria; nephritic syndrome (hematuria, decrease in GFR, oliguria, hypertension, edema); nephrotic syndrome (proteinuria >40 mg/m²/h, hypoalbuminemia, hyperlipidemia, and edema). Histopathologic examination was done by the same pathologist. Renal biopsies, all of which contained at least ten glomeruli, were processed for light and immunofluorescence microscopy. In light microscopy, biopsies were graded from I to V in increasing severity according to the Hass classification⁷ grades as follows: Grade I, normal histology or mild increase in mesangial matrix, without segmental lesions; Grade II, focal and segmental glomerular sclerosis, without glomerular hypercellularity or crescents; Grade III, focal (involving ≤50% of glomeruli present, exclusive of globally sclerotic glomeruli) mesangial and/or endocapillary proliferative glomerulonephritis; Grade IV, diffuse (involving >50% of glomeruli present, exclusive of globally sclerotic glomeruli) mesangial and/or endocapillary

proliferative glomerulonephritis; Grade V, advanced chronic glomerulonephritis, characterized by ≥40% globally sclerotic glomeruli and/or ≥40% interstitial fibrosis/tubular atrophy in the cortical tissue present, regardless of other histologic features. Mesangial IgA deposits are the defining hallmark of the disease in immunofluorescence microscopy.

Patients were placed into one of three treatment groups, as follows: (1) patients with recurrent macroscopic hematuria without proteinuria, and with normal kidney function, were treated with nonspecific therapy (omega-3:fish oil); (2) patients with proteinuria (range 0.5–3 g/1.73 m²/day) with or without microscopic hematuria had angiotensin converting enzyme inhibitors (ACEIs) and fish oil; and (3) patients with nephrotic syndrome had corticosteroid therapy (prednisolone or pulse methylprednisolone). Cytotoxic therapy was given when no response was observed following corticosteroid therapy.

Clinical outcome was graded as follows: A, normal (no hypertension, no urinary abnormality and no protein excretion and normal plasma creatinine concentration); B, minor urinary abnormalities (proteinuria <1 g/1.73 m²/day with or without microscopic-recurrent macroscopic hematuria); C, active renal disease (proteinuria >1 g/1.73 m²/day and/or elevated plasma creatinine level); or D, renal insufficiency (GFR <60 mL/min/1.73 m²).

Statistical analysis

Categorical data and proportions were compared using the chi-square test or Fisher's exact test, as indicated. Means were compared by Student's *t*-test, and medians were compared using the Mann–Whitney U test. The Kruskal–Wallis test was applied to the ordinal variables. A value of *P* < 0.05 was considered statistically significant. SPSS (v 11.0; SPSS Inc, Chicago, IL) software was used for statistical analysis.

Results

A total of 39 patients were included in the study. The mean follow-up time (± standard deviation [SD]) was 10.4 ± 3.51 (range 5–16) years. Twenty-nine (74.4%) were male and ten (25.6%) female. Males were affected more often than females (males:females = 3:1). The mean age (±SD) of the patients at onset of the disease was 9.5 ± 3.75 years (range 4–17). Elevated serum creatinine and hypertension were detected in 7.7% and 10.3% of patients, respectively. Nineteen (48.7%) patients presented with recurrent macroscopic hematuria, ten (25.6%) with microscopic hematuria ± proteinuria, six (15.4%) with nephritic syndrome, and four (10.3%) with nephrotic syndrome. The demographic and clinical findings of patients are shown in Table 1.

Table 1 The demographic and clinical features in 39 children with immunoglobulin A nephropathy

Features	n
Age at initial onset (year)	9.5 ± 3.75 (4–17)
Mean ± SD (range)	
Sex	
Male/female	29/10
High levels of serum IgA (n [%])	16 (41)
Recurrent macroscopic hematuria (n [%])	19 (48.7)
Hematuria ± proteinuria (n [%])	10 (25.6)
Nephritic syndrome (n [%])	6 (15.4)
Nephrotic syndrome (n [%])	4 (10.3)

All patients underwent renal biopsy. Immunofluorescence study showed IgA deposition in the glomerular mesangium in all specimens. Light microscopic findings of biopsies were: 22 (56.4%) patients, Grade I; four (10.2%), Grade II; eleven (28.3%), Grade III; and two (5.1%), Grade IV. There were no patients in advanced chronic glomerulonephritis (Grade V).

All patients in the study received fish oil after diagnosis. Twenty-nine (74.4%) patients were treated with ACEIs, and ten (25.6%) with corticosteroids. Three (7.7%) patients had corticosteroid plus cytotoxic agents including cyclosporine-A, cyclophosphamide, and azathiopurine. Four patients with nephrotic syndrome, three patients with nephritic syndrome, two patients with hematuria ± proteinuria, and one patient with recurrent macroscopic hematuria were given steroid therapy (Table 2).

At the end of follow-up time, 18 (46.1%) patients were normal, 15 (38.5%) had minor urinary abnormalities, three (7.7%) had active renal disease, and three (7.7%) developed renal failure. The relationship between initial clinical findings, biopsy findings, and outcomes of the patients is shown in Table 3.

All patients were evaluated according to risk factors at admission. Three patients with elevated serum creatinine

levels presented with recurrent macroscopic hematuria. These patients had Grade III renal biopsy specimens. Two of these patients entered remission while one had minor urinary abnormalities at last follow-up time.

Four (10.3%) of 39 patients had hypertension on admission. Two patients presented with recurrent macroscopic hematuria, and two with microscopic hematuria ± proteinuria. Three patients had Grade I, one had Grade IV. One of these four patients achieved remission, one had minor urinary abnormalities, one had active renal disease, and one developed renal failure at last follow-up (Table 4).

At onset, 20 patients had proteinuria (>1 g/day). Two of these had active renal disease while two developed renal failure at last follow-up time.

Discussion

This study evaluated initial clinical features, treatment modalities, and outcome in children with IgAN. Thirty-nine patients with IgAN were retrospectively reviewed over a 15-year period.

IgAN occurs at all ages but is most common during the second and third decades of life and uncommon in those under the age of 3 years.^{6,8} The peak incidence of IgA nephropathy in children occurs between 9 and 10 years of age.² In the present study, the mean age at disease onset was 9.5 ± 3.7 years. Primary IgAN is more frequent in males than females.² The male to female ratio in this study was 3:1.

The clinical presentation of IgAN is not pathognomonic. Asymptomatic microscopic hematuria can be found in 60% of subjects. Recurrent macroscopic hematuria continues to occur in 20%–80% of these patients.^{1,9,10} Some cases may present with acute nephritic syndrome and acute renal failure.⁶ In the present study, patients presented with recurrent macroscopic hematuria, microscopic hematuria ± proteinuria, nephritic syndrome, and nephrotic syndrome (48.7%, 25.6%, 15.4%, 10.3%, respectively). It is suggested that recurrent

Table 2 Outcome of patients given steroid treatment

Initial presentation		Treatment	Outcome*
Nephrotic syndrome (n = 4)	2 patients	ACEIs + fish oil + steroid + CA**	D
	1 patient	ACEIs + fish oil + steroid	C
	1 patient	ACEIs + fish oil + steroid	A
Nephritic syndrome (n = 3)	2 patients	ACEIs + fish oil + steroid	B
	1 patient	ACEIs + fish oil + steroid	A
Hematuria ± proteinuria (n = 2)	1 patient	ACEIs + fish oil + steroid + CA**	D
	1 patient	ACEIs + fish oil + steroid	C
Recurrent macroscopic hematuria (n = 1)	1 patient	ACEIs + fish oil + steroid	C

Notes: *Outcome: A, normal; B, minor urinary abnormalities; C, active renal disease; D, end-stage renal disease; **cytotoxic agents (CA): cyclosporine-A, cyclophosphamide, azathiopurine.

Table 3 Clinical findings, biopsy findings, and outcome results of all patients

Initial clinical findings	Biopsy	Outcome*			
		A	B	C	D
Recurrent macroscopic hematuria (n = 19)	Grade I	6	4	-	-
	Grade II	1	1	-	-
	Grade III	2	5	-	-
Hematuria ± proteinuria (n = 10)	Grade I	3	2	1	1
	Grade III	2	-	-	-
	Grade IV	-	1	-	-
Nephritic syndrome (n = 6)	Grade I	3	1	-	-
	Grade II	-	1	1	-
Nephrotic syndrome (n = 4)	Grade I	1	-	-	-
	Grade III	-	-	1	1
	Grade IV	-	-	-	1

Note: *Outcome: A, normal; B, minor urinary abnormalities; C, active renal disease; D, end-stage renal disease.

macroscopic hematuria is the most important presentation and seen more often than acute renal failure, a result similar to studies from Europe and United States.⁶

Hypertension is infrequently present at disease onset and, when present, is usually mild to moderate in severity and relatively easy to control.^{1,2} Likewise, decreased renal function rarely presents at disease onset.⁹ Ronkainen et al reported that hypertension at onset was present in 13% of the patients.¹ Hypertension at onset was not common in the present series: only four (10.3%) of the 39 patients had hypertension. One of these developed ESRD and another one had persistent, active renal disease at the end of follow-up. Three (7.7%) of the 39 patients had elevated serum creatinine at onset. Patients who present with hypertension at disease onset should receive careful follow-up.

In the literature, higher serum IgA levels were detected in 35%-70% of patients with IgAN.^{6,10} This marker may suggest the possible presence of disease. High levels of IgA are found during the phases of clinical activity.¹¹ In the present study, 41% of patients had elevated serum IgA at onset of disease.

The range of pathologic features of IgAN has been well described. Hass found that the most common histological lesions are focal proliferative glomerulonephritis, accounting for between 40% and 50% in both adults and children.⁷ In the Hass study, biopsies showing normal histology were more common in children than in adults (27%, 14%, respectively).⁷ In immunofluorescence microscopy, mesangial diffuse IgA deposits are the defining hallmark of the disease.¹² Immunoglobulin G, immunoglobulin M, and Complement 3 deposition may accompany IgA.¹³ In the present study, renal biopsy was performed in all patients. The immunofluorescence study showed IgA deposition in the glomerular mesangium in all specimens. Minimal histologic lesion (Grade I) was most commonly seen in the patients (56.4%). Focal proliferative glomerulonephritis (Grade III) and focal segmental glomerular sclerosis without proliferation (Grade II) accounted for 28.4% and 10.2%, respectively. Eleven patients in the study had diffuse proliferative findings (Grade III) and seven presented with recurrent macroscopic hematuria at onset of disease. These results suggest that first clinical findings are not related to renal biopsy findings. Therefore, patients with IgAN should undergo renal biopsy irrespective of initial symptoms.

The optimal approach to the treatment of IgA nephropathy is still uncertain. There are four separate approaches to IgA nephropathy:¹⁴⁻¹⁶ (1) patients with recurrent macroscopic hematuria with normal renal function, no proteinuria, and no microscopic hematuria between episodes are treated with nonspecific therapy (fish oil); (2) patients with persistent proteinuria (0.5–1 g/1.73 m²/day) ± microscopic hematuria might be treated with ACEIs; (3) patients with proteinuria (1–3 g/1.73 m²/day) persisting, despite ACEI/angiotensin receptor–blocker therapy, are treated with corticosteroid; and (4) patients with proteinuria (>3.5 g/1.73 m²/day) and/or rising serum creatinine, and/or renal biopsy with more severe histologic findings may benefit from immunosuppressive

Table 4 Patients with elevated serum creatinine and hypertension at onset

	Initial presentation		Biopsy	Therapy	Outcome*
Elevated serum creatinine	Recurrent macroscopic hematuria	Patient 1	Grade III	ACEIs + fish oil	B
		Patient 2	Grade III	ACEIs + fish oil	A
		Patient 3	Grade III	ACEIs + fish oil	A
Hypertension	Recurrent macroscopic hematuria	Patient 1	Grade I	ACEIs + fish oil	A
		Patient 2	Grade I	ACEIs + fish oil	B
	Microscopic hematuria ± proteinuria	Patient 1	Grade IV	ACEIs + fish oil + steroid	C
		Patient 2	Grade I	ACEIs + fish oil + steroid + CA**	D

Notes: *Outcome: A, normal; B, minor urinary abnormalities; C, active renal disease; D, end-stage renal disease; **cytotoxic agents (CA): cyclosporine-A, cyclophosphamide, azathiopurine.

Abbreviation: ACEIs, angiotensin converting enzyme inhibitors.

therapy in addition to corticosteroids. Donadio et al provided evidence that those patients who received omega 3 fatty acids (fish oil) for 2 years had a good prognosis.¹⁷ Hogg et al found parallel results.¹⁸ The lack of any significant side-effects and the potential for benefit make omega 3 fatty acid preparations an attractive initial option for patients with IgAN and proteinuria.¹⁹ Previous studies have shown that ACEIs alone or with angiotensin receptor–blocker therapy prevent progression of renal disease in patients with IgAN.^{20,21}

All patients in the present study were treated with fish oil after diagnosis. Twenty-nine of 39 patients (74.4%) were treated with ACEIs, and ten (25.6%) with corticosteroids. Three (7.7%) patients had corticosteroid plus cytotoxic agents including cyclosporine-A, cyclophosphamide, and azathiopurine. Four patients with nephrotic syndrome, three patients with nephritic syndrome, two patients with hematuria ± proteinuria and one patient with recurrent macroscopic hematuria were given steroid therapy.

IgAN was initially thought to follow a benign course, but it is now recognized that slow progression to ESRD occurs in up to 50% of affected patients.^{16,22} The remaining patients enter a sustained clinical remission or have persistent low-grade hematuria or proteinuria.²² However, the prognosis is quite variable and the outcome difficult to predict with accuracy in individual patients. In the European Renal Association chronic dialysis program for young adults, 22% of patients were under 30 years of age.²³ Short-term follow-up studies have shown a better prognosis for children, although long-term follow-up shows that IgAN in children is as progressive as in adults.^{4,24,25} Long-term studies have concluded that complete remission occurs in 5%–30% of patients.¹⁰ The majority of children with IgAN in this study admitted with macroscopic hematuria were found to have a good prognosis. In this study, 18 patients (46.1%) entered remission, which is a significantly higher proportion than in other studies reported to date.^{14,15}

In 2004, the International IgA Nephropathy Network and the Renal Pathology Society established a working group to develop an international consensus on practical histopathological classification of IgAN.^{26,27} The Oxford classification is the largest-scale histopathological study of IgA nephropathy.^{26,27} This classification provides substantially stronger evidence for a histopathological grading system to predict renal prognosis of IgA nephropathy. Compared with the previous classifications, in the present study the Oxford classification was found to be practical and useful.

In children with progressive IgAN, the clinical course is often slow.¹⁶ Among the factors that determine progression over

the years are reduced renal function, persistent hypertension, and proteinuria at onset.^{28–30} Four patients had hypertension at onset. One of these achieved remission, one had minor urinary abnormalities, and one had active renal disease while one developed renal failure. Twenty patients had proteinuria (>1 g/day) at onset. Two of these had active renal disease while two developed renal failure. Patients initially presenting with high serum creatinine levels, excepting those who had nephritic presentations, did not show poor prognosis, as the creatinine levels of all these patients were regressed to normal ranges shortly after disease onset. None had active renal disease, or developed renal failure at last follow-up. However, the authors believe that careful monitoring of these patients should continue.

Conclusion

The outcome results of the patients in this study are better than those reported in most other studies. Early diagnosis and treatment of IgAN in childhood may bring important benefits and a favorable prognosis. The majority of children with IgAN in this study were admitted with recurrent macroscopic hematuria, which was found to have a good prognosis. In addition, this study has shown that histopathological findings do not correlate with the course of the disease and progress of chronic renal failure. Steroids are still important agents in the treatment of IgA nephropathy. If patients with hypertension, elevated creatinine levels, or proteinuria are identified and receive early treatment, the course of disease can be modified and most patients will have a favorable prognosis.

Disclosure

The authors declare no conflicts of interest in this work.

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