

CLINICAL AND SEROLOGICAL FEATURES OF MESANGIAL IgA GLOMERULONEPHRITIS

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Summary

IgA-glomerulonephritis (IgA-GN) accounts for approximately 20 per cent of all glomerulonephritis in our unit. Seventeen out of 50 patients with IgA-GN developed renal failure, which appeared in 11 out of 17 over the course of a mean follow-up of 68 months. Haemodialysis was required in three patients. Twenty-two out of 50 patients had hypertension, five with malignant hypertension. Perivascular IgA deposits were found in skin biopsies of 29 per cent of patients with IgA-GN and also in 19 per cent of patients with other GN, but not in healthy controls. Mucosal (salivary and nasal) secretory IgA concentrations were normal. In cutaneous and glomerular IgA/IgM deposits, IgA₁ was demonstrated using monoclonal antibodies. No excess of HLA-A, B or DR antigens and no relation of clinical course and HLA-Bw35 were found.

Introduction

The present communication gives the salient features of the clinical and immunological findings in 50 consecutive cases of biopsy-confirmed mesangial IgA-GN observed in our unit.

Patients and methods

Fifty patients, aged 16–61 years (median 33 years; 12 female, 38 male) with biopsy-confirmed mesangial IgA-GN without arthralgia, purpura, GI-symptoms or liver disease were studied. The following procedures were undertaken: skin biopsy from the medial aspect of the thigh; immunofluorescence (IF) with monospecific FITC conjugates (Behring Co, own preparation). Serum-IgA with Beckmann IC-nephelometer; circulating IgG, IgA immune complexes (IC) with Raji-assay, RSL-assay and Clq-PEG assay; determination of cell bound complexes with ¹²⁵I antihuman IgA F(ab)₂ of sheep (purified by immunoabsorption). Secretory IgA in nasal washings and saliva by ELISA using colostrum

sIgA standard. IgA subclass analysis by indirect IF, using monoclonal IgA₁ and IgA₂ ab (Becton Dickinson Lab, Sunnyvale, California). FITC conjugated anti-mouse F(ab)₂ as second ab (Targo Inc, Burlingame, California) (did not stain normal or abnormal renal tissue in absence of mouse antihuman ab). Rabbit antihuman J chain antisera (Nordic Immunological Lab, Tilberg, Netherlands); goat antirabbit IgG (Dakopatts, Denmark). HLA-A, B, C, DR with microcytotoxicity test after Terasaki. Data as $\bar{x} \pm SD$; statistics with Fisher's exact test.

Results and discussion

Epidemiology

In 1979–1981, on the basis of renal biopsy, glomerulonephritis (GN) was diagnosed in 160 consecutive patients, 32 of whom had IgA-GN (20%). This proportion is in agreement with recent reports of a high incidence of IgA-GN [1–4].

Salient clinical features

Impaired renal function (serum creatinine >1.4mg/dl) was observed in 17 out of 50 patients (34%). Eleven out of 17 patients had normal function at the time of biopsy and developed renal failure during follow-up (4–186 months, median 68 months). Three patients progressed to dialysis. Nineteen out of 50 patients were hypertensive at the time of biopsy and 22 out of 50 (44%) had hypertension at the time of the study. No less than five patients had malignant hypertension (retinal haemorrhage and cotton wool exudate).

IgA in skin biopsy – specific finding?

The occurrence of vascular IgA-deposits in clinically normal forearm skin of patients with IgA-GN has been noted [5,6]. Such deposits are evidence of the systemic nature of IgA-GN which is also illustrated by the occurrence of scleritis [7] and IgA-deposits in muscular vessels [8]. We examined dermal biopsies (medial aspect of the thigh) in 41 patients with IgA-GN, 21 with biopsy confirmed GN other than IgA-GN and 50 healthy volunteers. Perivascular deposits were found in: IgA-GN 12/41 (29%), other GN 4/21 (19%) controls 0/51 (0%). This observation indicated that perivascular IgA-deposits are common in GN, but not specific for IgA-GN.

Characterisation of glomerular and skin IgA-deposits

In 14 renal biopsies and IgA positive skin biopsies (n=10) incubation with monoclonal antibodies consistently showed IgA₁ deposits in glomeruli or perivascular sites. Only trace amounts of IgA₂ were found in two glomeruli (renal biopsies) and two skin biopsies. Both IgA₁ and IgA₂ were constantly found in casts, similar to the study of Conley [9]. Cutaneous and glomerular IgA/IgM deposits stained with J chain ab. On the other hand, with monospecific Nordic Co anti-

sera, as used in the study of André [10], IgA₂ was found in five patients, IgA₁ in one patient and both IgA₁ and IgA₂ in one patient, probably reflecting the limited specificity of the antiserum.

Serum IgA and IgA-immune complexes (IC) and secretory IgA in mucosal secretions

Elevated IgA concentrations (>312mg/dl) were found in 22 out of 41 patients (54%). In individual patients, serum IgA values changed little with time. Circulating IgA-IC (>20μEq/ml – Raji test) were found in eight out of 33 patients (24%). It cannot be excluded, however, that IgA-IC, as measured with our assays, represent polymeric IgA rather than IgA-IC.

No relationship was observed between serum creatinine or blood pressure and serum IgA or IgA-IC. Serum IgA was similar in patients with and without perivascular IgA deposits in the skin. IgG or IgA concentrations (immuno-diffusion with LC-Partigen plates) and secretory IgA (ELISA) in salivary fluid and nasal washings were similar in healthy controls and IgA-GN (salivary sIgA controls 69.9 ± 50.1mg/L, n=26; IgA-GN 42.9 ± 35.6, n=10 – NS).

HLA-types – prevalence and relation to clinical course

Greater prevalence of HLA-Bw35 in patients with IgA-GN [11] and segregation with HLA-Bw35 in family studies [12], although not confirmed by all investigators [13,14] suggests some role for HLA-Bw35. There are also reports of a higher prevalence of HLA-B12 [13] but again reports to the contrary exist. On the basis of population studies [15] and family studies [16] an association of IgA-GN and DR4 has been proposed. Finally, it has been suggested that HLA-Bw35 represents a marker of poor prognosis [17].

In agreement with recent findings of Mustonen [18] we failed to observe an excess of any of the HLA-B or DR-antigens. Specifically, HLA-B12, HLA-Bw35 and HLA-DR4 showed no correlation with the clinical course (blood pressure, serum creatinine). There was a suggestion of an adverse influence of HLA-B7 (5/10 patients with HLA-B7 had renal failure; 2/10 malignant hypertension), but in view of the sample size this must remain speculative.

TABLE I. HLA-antigens in IgA-GN

	IgA-GN	General population
B7	27.8%	16%
B12	33.3%	23%
Bw35	16.7%	14%
DR1	30.0%	16%
DR2	23.2%	22%
DR3	13.3%	19%
DR4	16.7%	26%
DR5	30.0%	18%
DRw6	16.7%	7%
DR7	6.7%	21%

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Open Discussion

MATOUŠOVIC (Prague) Are there, in your opinion, any immunofluorescence signs which are of prognostic importance. Our findings in 26 patients suggest that the absence of fibrin deposition in glomerular mesangium results in a benign course whilst its presence correlates with a more serious course in IgA nephropathy.

RAMBAUSEK We have not found any correlation between the immunoglobulin deposits and the course of these patients.

MATOUŠOVIC Our follow-up was for five years and we had very strong correlation.

HENE (Utrecht) You told us that there was a better prognosis in patients with microscopic haematuria. Perhaps you should wait longer because we found three patients with microscopic haematuria 23 years before they developed renal failure. The natural history of the disease may be very long.

RAMBAUSEK That is right.

IHLE (Melbourne) I agree with you it is a very common disease. Our experience is that it is the single most common form of glomerulonephritis leading to end-

stage renal failure. We have found that in patients who have recurrent bouts of macroscopic haematuria or persistent microscopic haematuria of up to one million red cells, based on the Fairley phase-contrast method, there is a high incidence of crescent formation in association with IgA nephropathy. I wonder whether you have any similar experience with regards the relationship of the biopsy finding to haematuria and crescent formation?

RAMBAUSEK No, there was no correlation.

D'AMICO (Milan) In more than 50 patients with idiopathic IgA nephropathy we did not find the skin vascular IgA deposits that you and the Flemish authors (Baart-de-la-Faille et al) found. On the contrary we found these deposits in Henoch-Schonlein disease. Also French authors, according to personal communications from L Morel-Maroger and R Habib in Paris, have not found these extrarenal deposits. Is this difference in the extrarenal expression of IgA nephropathy in Latin countries of southern Europe and in countries of northern Europe (Holland and Germany) due to a difference in the kind of disease we are observing? This could also explain the higher percentage of malignant hypertension and of progression to uraemia that you and some Flemish authors (Van Der Peet et al) observe in comparison with authors from Italy and France.

MERY (Chairman) There may be some slight differences even in Prussian groups and the results that Dr Habib has told you are maybe in children but we had the same experience in adults in Paris as Dr Rambausek had in Germany.

ZUCCELLI (Bologna) You found increased amounts of polymeric IgA in the serum of your patients. Did you correlate the presence of polymeric IgA with the clinical course?

RAMBAUSEK We did not find any correlation.

MERY (Chairman) We have recently seen two patients in whom IgA nephropathy was associated with ankylosing spondylitis and we are aware of two other cases in the two different Prussian groups and we could find seven similar cases reported and I think that these eleven cases make it difficult to think that the association is just occasional. I would like to ask you if you have seen any patients with the association of IgA nephropathy and ankylosing spondylitis?

RAMBAUSEK No, I do not remember having seen such a patient.

MERY (Chairman) I would like to ask the audience if anyone has seen this association?

RITZ (Heidelberg) When the first reports from Clinton came out I was of course anxious to look at this and as a matter of fact there is a remarkable incidence of proteinuria in patients with ankylosing spondylitis. Unfortunately, I was unable to biopsy them for ethical and compliance reasons, but I think

there is some relation. I think in a broader prospective the association has been reported with bronchial carcinoma and with mycosis fungoides. I think all this points to what Dr D'Amico so beautifully points out, disturbed immune regulation in this disease is a pre-conditioning factor in the genesis of IgA glomerulonephritis.

MERY (Chairman) Yes, you are right, but it is interesting because as you know serum IgA is often elevated in ankylosing spondylitis so that might be a link between the two diseases.

RITZ (Heidelberg) I can confirm proteinuria but not IgA nephropathy.

MERY Yes, but proteinuria might be due to many other causes such as amyloidosis.