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Age-Related Histologic Alterations after Prednisolone Therapy in Children with IgA Nephropathy

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TANAKA, H., WAGA, S. and YOKOYAMA, M. *Age-Related Histologic Alterations after Prednisolone Therapy in Children with IgA Nephropathy.* Tohoku J. Exp. Med., 1998, **185** (4), 247-252 —— To examine whether the age of onset of clinical symptoms in childhood IgA nephropathy may affect changes of histologic alterations after receiving prednisolone therapy, an evaluation of glomerular lesions seen in biopsy specimen was done. Eighteen children with IgA nephropathy met study criteria. They received alternate-day prednisolone therapy within a month after the first renal biopsy. Renal biopsies were done at presentation and repeated at a mean interval of 23 months. The patients were grouped as follows: Group A, 8 cases which showed clinical symptoms at the age of 9 or under; Group B, 10 cases which showed the symptoms at the age of 10 or over. At the initial presentation, hitologic indices including a percentage of mesangial area occupying glomeruli (the M/G ratio) in the 2 groups did not show a significant difference. The activity score and the M/G ratio in the group A decreased significantly at the second biopsies (4.6 ± 0.9 vs. 1.8 ± 1.0 and $25.7 \pm 6.1\%$ vs. $21.4 \pm 2.7\%$, respectively), while in the group B did not. These observations may indicate the age of onset of clinical symptoms in childhood IgA nephropathy affects changes of histologic alterations after receiving prednisolone therapy. ———— age-related character; childhood IgA nephropathy; histologic alterations; mesangial matrix area; prednisolone therapy

Childhood IgA nephropathy is now recognized to have a variable clinical courses, from spontaneous remission to progression to renal death (Kusumoto et al. 1987; Yoshikawa et al. 1987b; Hogg et al. 1994; Wyatt et al. 1995). Concerning the age at the onset of clinical symptoms in childhood IgA nephropathy, Yoshikawa et al. (1987b) observed that children with a later onset of symptoms (children aged 9 years or more) are more likely to develop an renal failure than children with a early onset. Shigematsu et al. (1990) reported that age-related character of the histologic lesions in IgA nephropathy, namely lesser glomerular sclerosis and segmental lesions in patients with an earlier onset are seen. Yoshikawa et al. (1987a) reported that characteristic early lesions of predominant

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mesangial hypercellularity in childhood IgA nephropathy changes to a gradual matrix increase, according to the disease progression. Recent studies suggested that increase of mesangial matrix correlate with unfavorable outcome in IgA nephropathy (Tateno and Kobayashi 1987; Suzuki et al. 1990; Tanaka et al. 1998b).

In previous papers, we demonstrated that prednisolone therapy may ameliorate the histologic inflammatory process and suppress subsequent increase of mesangial matrix in children with proteinuric IgA nephropathy (Tanaka et al. 1998a and b). For this paper, we examined whether the age of the onset of clinical symptoms in children with IgA nephropathy may affect changes of histologic alterations after receiving prednisolone therapy.

Patients and Methods

Patients. A total of 18 children with primary IgA nephropathy, who received alternate-day prednisolone therapy without cytotoxic agents (Tanaka et al. 1998a) within a month after the first renal biopsy, and repeat renal biopsy at a mean interval of 23 months from the first renal biopsy enrolled the study. Of the 18 patients, 8 (3 boys, 5 girls) were 9 years old or under (Group A) and the remaining 10 (6 boys, 4 girls) were 10 years old or over (Group B) at the first visit to our hospital. Twelve of these patients were referred to our hospital after a mass urine screening test for school children with positive for urinary protein. Of the remaining study participants, 4 visited our hospital with gross hematuria, 2 presented with acute nephritic or nephrotic syndrome. No patient showed renal impairment or hypertension at the initial presentation. A percutaneous renal biopsy was done within a year in all cases.

An alternate-day prednisolone regimen (initial dosage 1 mg/kg, maximum 60 mg) started within a month after the diagnosis had been made in all cases. Our indication for prednisolone therapy was based on such observations as persistent and moderate proteinuria with hematuria, and diffuse histologic alterations associated with moderate mesangial cell proliferation (Tanaka et al. 1998b). The dosage of prednisolone gradually tapered and the therapy was continued for 2 years (Tanaka et al. 1998a).

Methods. Individual 24-hour urine protein excretion (g/day) and creatinine clearance data and histologic alterations seen in the renal biopsy samples were evaluated as reported previously (Tanaka et al. 1998a and b). In breif, periodic acid-Schiff-stained specimens were scored blindly, using a scoring system described by Andreoli and Bergstein (1989). The activity score was determined by grading mesangial cell proliferarion on a scale of 0 to 3 (none=0, mild=1, moderate=2, severe=3), interstitial mononuclear cell infiltration on a scale of 0 to 3, and crescent formation on a scale of 0 to 3, according to the percentage (0%=0, 1-20%=1, 21-50%=2, >50%=3) of glomeruli involved. The chronicity score was determined by counting the number of glomeruli demonstrating fibrous

crescents and segmental or global sclerosis, and each was scored on a scale of 0 to 3, according to the percentage of glomeruli involved, as indicated. Tubular atrophy and interstitial fibrosis were each scored on a scale of 0 to 3. The sum of these numbers comprised the activity score (maximum=9) and the chronicity score (maximum=12), respectively.

A measurement of mesangial matrix area occupying the glomerulus was performed by using the modified method described by Tateno and Kobayashi (1987) and reported previously (Tanaka et al. 1998a and b). In breif, the outer margin of capillary tufts and the periodic acid-Schiff-positive area, shown in photomicrographs (130×90 mm) of stained glomeruli, were demarcated with fine lines by a computer-linked digitizer (Picture Analyzer, model Σ5/E; Medical System Reseach, Tokyo). The demarcated areas were measured, and then percentage of mesangial matrix area occupying the selected glomeruli was calulated M/G ratio. The mean percentage were calculated for 3 or more glomeruli. Glomeruli with crescents, sclerosis or tuft adhesion, or that were not cut in an equatorial line, were excluded from the examination. The coefficient of variation in these measurement was 1.1% (Tanaka et al. 1998a).

Data were expressed as mean±standard deviation, and analyzed by one-way analysis of variance and Wilcoxon U test using Stat View™ SE+Graphics, Version 1.04 (Abacus Concepts, Berkeley, CA, USA) computer software. A p-value of less than 0.05 was considered statistically significant.

Results

Mean urine protein excretion and the histologic indices (the activity score, the chronicity score, the M/G ratio) at the first biopsies did not show a statistical difference between the group A and B (1.1±1.1 g/day vs. 0.7±0.4 g/day in mean urine protein excretion, 4.6±0.9 vs. 3.7±1.3 in the activity score, 4.0±1.3 vs. 4.6±1.6 in the chronicity score and 25.7±6.1 % vs. 22.1±2.2% in the M/G ratio, respectively). A mean interval between the first and second renal biopsies did not show a significant difference between the 2 groups (19.8±12.2 months vs. 26.2±24.1 months). The changes in these indices in the group A are shown in Table 1. When measured at a mean interval of 20 months from the first examination, urine protein excretion, the activity score and the M/G ratio showed a significant decrease. The chronicity score did decrease but not significantly. The changes in these indices in the group B are shown in Table 2. In the group B, mean urine protein excretion and these histologic indices showed a decreasing tendency but not significantly. After a mean follow-up of 55 months, none of the study patients showed a progression to renal insufficiency.

Discussion

Although an appropriate therapeutic strategy for the suppression of disease progression in childhood IgA nephropathy has not been established, corticosteroid

TABLE 1. *First and second renal biopsy results in 8 patients with IgA nephropathy who showed clinical symptoms at the age of 9 or under (Group A).*

Variable	1st renal biopsy	2nd renal biopsy[a]
Proteinuria (g/day)	1.1±1.1	0.3±0.4*
Activity score	4.6±0.9	1.8±1.0*
Chronicity score	4.0±1.3	3.2±1.5
M/G (%)	25.7±6.1	21.4±2.7*

M/G, mean percentage of mesangial areas occupying the glomeruli; Values given are means and S.D.

[a]Second biopsy was performed a mean of 20 months aftr the first one.

*$p<0.05$

TABLE 2. *First and second renal biopsy results in 10 patients with IgA nephropathy who showed clinical symptoms at the age of 11 or over (Group B).*

Variable	1st renal biopsy	2nd renal biopsy[a]
Proteinuria (g/day)	0.7±0.4	0.4±0.2
Activity score	3.7±1.3	2.6±1.0
Chronicity score	4.6±1.6	4.2±1.3
M/G (%)	22.1±2.2	23.1±4.9

M/G, mean prcentage of mesangial areas occupying the glomeruli; Values given are means and S.D.

[a]Second biopsy was performed a mean of 26 months after the first one.

therapy has been reported to be of benefit in ameliorating disease activity (Andreoli and Bergstein 1989; Waldo et al. 1993; Tanaka et al. 1998a). Therefore, we had been conducting prednisolone therapy in children with IgA nephropathy, basing therapy on the premise that a significant inflammatory injury might occur in the progression of IgA nephropathy, and reported that the importance of the initiation of prednisolone therapy in children with proteinuric IgA nephropathy in the early stages of the disease to prevent increase of mesangial matrix and succeeding renal insufficiency (Tanaka et al. 1998a and b).

Meanwhile, a variety of clinical courses of childhood IgA nephropathy from spontaneous remission to progression to renal failure have been known. Yoshikawa et al. (1987b) reported that children with a younger onset of IgA nephropathy have a tendency to be favorable outcome. Hogg et al. (1994) reported that the rate of progression of disease is slower in the 6 younger patients with IgA nephropathy after a 5-year observation. Concerning age-related character of hitologic alterations in IgA nephropathy, Shigematsu et al. (1990) reported that lesser glomerular sclerosis was seen in the younger patients. Yoshikawa et al. (1987a) also reported that predominant mesangial hypercellularity without increase of mesangial matrix, which is thought as an early lesion in the disease, is

characteristic in childhood IgA nephropathy. Taken together, children with a younger onset of IgA nephropathy may have favorable outcome, partly because of lesser glomerular sclerosis and without mesangial matrix increase. These observations required us to examine whether the age of onset of clinical symptoms in children with IgA nephropathy may affect changes of histologic alterations after receiving prednisolone therapy, since early lesions such as mesangial cell hypercellularity is thought as a reversible lesion by the therapy (Tanaka et al. 1998b).

The present study demonstrates that mean urine protein excretion and the histologic indices, such as the activity score and the M/G ratio in patients aged under 9 years at the presentation, decreased significantly at the second renal biopsy. While in patients aged over 10 years at the presentation, those indices did decrease but not significantly. Since proteinuria and the histologic indices using in the present study were compatible with unfavorable parameters in IgA nephropathy (D'Amico et al. 1986; Kusumoto et al. 1987; Yoshikawa et al. 1987a; Hogg et al. 1994), a significant decrease in these indices in children with a younger onset may indicate favorable response to the prednisolone therapy than children with an older onset.

Although a decrease in proteinuria and the activity score may not indicate the effectiveness of the therapy, since a spontaneous remission cannot be excluded. However, the lack of increase in the M/G ratio and the chronicity score might indicate a beneficial effect of prednisolone therapy (Tanaka et al. 1998a). Moreover, a significant decrease in the M/G ratio seen in the group A but not in the group B, strongly suggested a favorable response to the therapy in the patients with a younger onset, since an increase in the M/G ratio correlates with an unfavorable outcome (Tateno and Kobayashi 1987; Tanaka et al. 1998b). Taking all the evidence together, it is suggested that the age of onset of IgA nephropathy affects changes of histologic alterations after receiving prednisolone therapy.

However, clinical outcome between the 2 groups were not different in the study, since no patients progressed to renal insufficiency after a mean follow-up of 55 months. It is difficult to draw long-term conclusions, because of the small number of patients examined and the short observation period of the study. Despite these limitations, it must be interesting to consider that the age of onset of clinical symptoms in childhood IgA nephropathy may affect changes of histologic alterations after receiving prednisolone therapy. Further study is needed to confirm these preliminary findings.

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