Pediatr Nephrol (2006) 21:194–200
DOI 10.1007/s00467-005-2074-7

ORIGINAL ARTICLE

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Long-term follow-up of atypical membranoproliferative glomerulonephritis: are steroids indicated?

Received: 1 April 2005 / Revised: 20 July 2005 / Accepted: 20 July 2005 / Published online: 25 October 2005

Abstract Atypical membranoproliferative glomerulonephritis (MPGN) has been reported to have a good prognosis when treated with corticosteroids. However, this recommendation is based on uncontrolled trials and is associated with many complications. The purpose of our study is to determine whether steroid therapy is indicated for atypical MPGN. The cases of seven patients with atypical MPGN are reported in this study. Urinary abnormalities of five of them were detected by urine screening at school, of two because of macrohematuria. Hypocomplementemia was noted in six patients. All but one patient were treated without corticosteroids, and five with angiotensin-converting enzyme inhibitors (ACEI) and/or the Chinese herbal medicine Sairei-to (TJ-114). One patient recovered spontaneously from proteinuria and was therefore not treated, and one who developed severe proteinuria during observation was treated with corticosteroids. After an average follow-up period of 10.0 years, five patients showed normal urinary findings, one had hematuria and one proteinuria. At the most recent follow-up, the renal function of all patients remained within the normal range, and serum C3 had returned to normal levels in five out of six. These findings suggest that the indication of steroid therapy for atypical MPGN should be re-examined, since most of the patients with atypical MPGN seem to have an excellent prognosis without treatment with corticosteroids.

Keywords Angiotensin-converting enzyme inhibitors · Atypical membranoproliferative glomerulonephritis · Prognosis · Steroid therapy · Typical membranoproliferative glomerulonephritis

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Introduction

In Japan, the results of widely performed urine screening of school children and renal biopsies performed for persistently hypocomplementemic children at an early stage have produced findings of atypical membranoproliferative glomerulonephritis (MPGN) and were recently reported by several authors [1, 2, 3, 4, 5, 6].

The outcomes of several clinical trials indicate that alternate-day steroid therapy, the most thoroughly investigated regimen for children with typical MPGN [7, 8, 9, 10, 11], is also used to treat children with atypical MPGN and seems to have a good prognosis [2, 5, 6, 12]. However, these findings are based on uncontrolled trials designed to demonstrate improved renal survival with steroid therapy. Moreover, steroid medication for children with MPGN is associated with many complications such as hypertension, hyperglycemia, growth retardation, ac-

Table 1 Profile of seven atypical MPGN children. *School US* school urinary screening; *MH* macrohematuria; *H* hematuria; *P* proteinuria. Degree of proteinuria graded: ±, 15 mg/dl; +, 30 mg/dl; ++, 100 mg/dl; +++, 300 mg/dl; C3 normal range: 65–135 mg/dl

Patient no.	Age/ sex	Initial presentation	Urinalysis at presentation	Urinalysis at renal biopsy	C3 at presentation (mg/dl)	C3 at renal biopsy (mg/dl)	Cr at presentation (mg/dl)	Period to biopsy (years)
1	6/M	School US	H/P(+)	H/P (++)	2.5	11.3	0.6	0.2
2	9/F	School US	H/P (+)	H/P (+)	72	90	0.5	0.7
3	9/M	School US	H	H/P (+)	24	18	0.36	1.1
4	11/F	School US	H	H	24	38	0.6	0.5
5	14/F	School US	H	H/P (+)	Not measured	8	0.58	2.2
6	8/F	MH	MH	MH/P (+)	5	32	0.5	0.3
7	9/M	MH	MH/P (+++)	MH/P (+)	42	43	0.5	0.2

celerated weight gain, gastrointestinal hemorrhage, glaucoma and cataracts [13, 14, 15, 16].

In this paper, we report the long-term clinical course of seven children with atypical MPGN treated without corticosteroids as the first treatment to determine whether steroid therapy is indicated for atypical MPGN.

Materials and methods

Patients

The records of all children with atypical MPGN who were evaluated between 1979 and 2002 by the pediatric nephrology service at Kobe University School of Medicine were reviewed. Potential secondary causes of MPGN, such as systemic lupus erythematosus, hepatitis B/C nephropathy, bacterial infection, partial lipodystrophy or Henoch-Schönlein purpura nephritis, were ruled out from all patients. The patients with hypocomplementemia and elevated antistreptolysin O (ASO) levels were observed without any treatment for more than 8 weeks to exclude the possibility of poststreptococcal acute glomerulonephritis (PSAGN), because the C3 level has been reported to return to normal after less than 8 weeks in the regular course of PSAGN [17, 18].

Pathological studies

The renal biopsies were performed with the percutaneous technique. Biopsy specimens for light microscopy (LM) were stained with hematoxylin-eosin (HE), periodic acid-Schiff (PAS) and periodic acid-methenamine silver stain (PAM). Tissue for immunofluorescence (IF) was stained with fluorescein-tagged antisera to human IgG, IgA, IgM, C1q, C3, C4 and fibrinogen. Tissue for electron microscopy (EM) was stained with uranyl acetate and lead citrate and was examined with a JEM-100S electron microscope.

The diagnosis of typical MPGN was based on the histological criteria specified by the International Study of Kidney Disease in Children (ISKDC) and the World Health Organization [19, 20]. The diagnosis of atypical MPGN was made with reference to the report described by Yoshikawa et al. [4] and was based on the following three criteria established with LM, IF and EM.

LM

Mesangial cell proliferation accompanied by an increase in mesangial matrix is seen in all or nearly all glomeruli. The thickening of the capillary wall, which sometimes has the appearance of a double contour, is focal and/or segmental distribution. Focal is defined as a lesion involving up to 50% of the glomeruli, and segmental as a lesion involving a portion of the glomerulus. However, a double-contoured appearance is not necessarily present in all cases. Some cases have only the histological features of diffuse mesangial proliferative glomerulonephritis.

IF

The deposits vary in amount, distribution and appearance and are located along the capillary wall and/or in the mesangium. C3 is almost invariably present, particularly as prominent granular mesangial deposits. Immunoglobulins are found less consistently, mainly IgG and IgM and occasionally IgA.

EM

The electron-dense deposits lie mainly in the mesangial and subendothelial areas and are occasionally observed in the subepithelial and intramembranous regions. The so-called mesangial interposition is not necessarily detected in all patients.

Definitions

Hematuria was defined as either a positive urine dipstick for blood or an erythrocyte excretion >10/mm^3 of uncentrifuged urine and macrohematuria if visible with the naked eye. Proteinuria was defined as a 1+ or higher reading on the dipstick and quantified by the urine protein-creatinine ratio of freshly voided urine [21, 22, 23]. The normal urinary protein-creatinine ratio was set at <0.2 mg/mg. Hypertension was defined when systolic and diastolic blood pressures exceeded the 95th percentile for age and gender. Nephrotic syndrome was defined as the presence of proteinuria (urine protein excretion >40 mg/m^2 per hour for a 12- to 24-h overnight collection) and serum albumin levels of less than 2.5 g/dl, acute renal insufficiency as a decreased glomerular filtration rate (GFR) to <60 ml/min per 1.73 m^2 and acute nephritic syndrome as hematuria accompanied by at least two of the following: hypertension, raised serum urea or creatinine levels and oliguria. Finally, hypocomplementemia was defined as serum C3 levels of less than 50 mg/dl (normal range: 65–135 mg/dl).

Results

Patient characteristics

Forty-two children (24 boys and 18 girls) were diagnosed as having MPGN by means of renal biopsy, 20 of whom could not be followed up. Among the 22 children who were diagnosed as having MPGN and have been followed up until now, 15 (10 boys and 5 girls) showed the pathological characteristics of typical MPGN and the remaining 7 (3 boys and 4 girls) showed the pathological

Table 2 Light microscopic and electron microscopic findings of seven patients with atypical MPGN. 0, absent; 1, slight; 2, moderate; 3, intense; *g* global; *s* segmental; *ND* not done

Patient no.	Period to biopsy (years)	Light microscopy						Electron microscopy				
		No. of glomeruli	Mesangial proliferation	Double contour		Crescent	Global sclerosis	Deposit				Mesangial interposition
				Segmental (%)	Global			Mesangial	Subendothelial	Subepithelial	Intramembranous	
1	0.2	21	Diffuse	3 (14%)	0	0	0	3+	1+	1+	-	1+
2	0.7	12	Diffuse	2 (17%)	0	4	1	1+	1+	-	-	1+
	4.8	10	-	0	0	0	0	ND	ND	ND	ND	ND
3	1.1	52	Diffuse	0	0	0	0	1+	1+	1+	-	1+
4	0.5	12	Diffuse	0	0	0	0	3+	1+	1+	-	-
5	2.2	18	Diffuse	0	0	0	0	3+	1+	-	-	-
	3.4	16	Focal	1 (6%)	0	0	0	3+	-	-	-	-
6	0.3	16	Diffuse	0	0	1	0	3+	1-2+	-	-	-
7	0.2	18	Focal	0	0	2	0	2-3+	-	1+	2+	-
	1.0	22	Diffuse	0	0	20	0	3+	-	1+	2+	-
	1.3	20	Diffuse	0	0	6	0	2+	1+	-	-	-
	3.0	22	Focal	0	0	0	1	2+	-	-	2+	-
	9.2	27	Diffuse	0	0	0	9	1+	1+	-	-	-

characteristics of atypical MPGN. The clinical characteristics of the seven children with atypical MPGN are shown in Table 1. The mean age at presentation was 9.4 years. No acute renal insufficiency or nephrotic syndrome was observed. Hypocomplementemia was noted in six patients (85.7%). ASO titers were elevated in only one patient (patient 6; ASO 787 IU/ml; normal range, under 265 IU/ml), who showed macrohematuria at presentation. However, she did not have any preceding infection nor did she show signs of hypertension, weight gain or edema. We observed her without any treatment, but hypocomplementemia (C3, 5 mg/dl at presentation) continued, and proteinuria also developed. Therefore, we performed a renal biopsy 3 months after the onset (Tables 2 and 3). Her clinical course and pathological findings were not typical of PSAGN, and she was diagnosed as having atypical MPGN.

Pathological studies

Histological data of all seven patients with atypical MPGN are listed in Tables 2 and 3. The mean interval between detection of the disease and renal biopsy was 0.7 years. The initial biopsy showed diffuse mesangial proliferation in six patients and focal mesangial proliferation in one. Segmental double-contoured appearance was observed in two patients. Electron-dense deposits in the mesangium were seen in all cases, and subendothelial dense deposits in six patients. Immunofluorescent studies showed C3 deposits in all seven biopsies in the capillary walls and/or mesangial areas. IgA was detected in two patients, but was less consistent than C3.

Treatment

All patients but one were treated without the use of corticosteroids, five of them with angiotensin-converting enzyme inhibitors (lisinopril) and/or the Chinese herbal medicine Sairei-to (TJ-114). One patient (patient 1) recovered spontaneously from proteinuria and thus was not treated (Table 4 and Fig. 1).

Only one patient (patient 7) was treated with corticosteroids. He was noted to have hypocomplementemia with a serum C3 level of 42 mg/dl at presentation, while the ASO titer was within the normal range. Since his clinical course was not typical of PSAGN, the first renal biopsy was performed 2 months after the detection of the urinary abnormalities. Light microscopy showed focal mesangial cell proliferation, but the double contoured appearance was not observed, while crescents were present in 2 of 18 glomeruli (11.1%). Immunofluorescent studies showed positive deposits of C3 along the capillary walls of the glomeruli, and electron microscopic examination disclosed the presence of mesangial, intramembranous and subepithelial electron-dense deposits along the glomerular basement membrane (GBM). No mesangial interposition was observed. On the basis of these

Table 3 Immunofluorescence studies of seven patients with atypical MPGN. 0= absent, 1= slight, 2= moderate, 3= intense; *g* global, *s* segmental; *ND* not done

Patient no.	Period to biopsy (years)	Immunofluorescence						
		C3	IgA	IgG	IgM	Clq	C4	Fibrinogen
		Capillary/mesangium						
1	0.2	3g/0	1 s/1 s	0/0	0/0	ND	0/0	1 g/0
2	0.7	0/2g	0/1 s	0/1 s	0/0	0/0	0/0	0/1 g
	4.8	0/0	0/0	0/1 s	0/0	0/0	0/0	0/1 s
3	1.1	3g/3g	0/0	1 s/0	0/0	0/0	0/0	1 g/1 g
4	0.5	0/2–3g	0/0	0/0	0/0	0/0	0/0	0/1 g
5	2.2	0/3g	0/0	0/1 s	0/1 s	0/0	0/0	0/2 g
	3.4	1s/3g	0/0	0/0	0/0	0/0	0/0	0/1 g
6	0.3	0/2g	0/0	0/0	0/0	0/0	0/0	1 g/1 g
7	0.2	1g/0	0/0	0/0	0/0	1 s/1 s	0/0	1 s/1 s
	1.0	0/2g	0/0	0/0	0/0	0/0	0/0	ND
	1.3	0/2g	0/0	0/0	0/1 g	0/0	0/0	1 s/1 s
	3.0	0/1g	0/0	0/0	0/0	0/0	0/0	0/0
	9.2	1s/1s	0/0	1g/0	1 s/1 s	0/0	1 s/1 s	0/0

Table 4 Treatment. *ACEI* angiotensin converting enzyme inhibitors; *mPSL* methylprednisolone, *PE* plasma exchange; *ALD* altemate-day prednisolone

Patient no.	Period to biopsy (years)	Treatment after biopsy
1	0.2	No therapy
2	0.7	Sairei-to + ACEI
	4.8	ACEI
3	1.1	ACEI
4	0.5	Sairei-to
5	2.2	Sairei-to
	3.4	Sairei-to + ACEI
6	0.3	Sairei-to
7	0.2	Dipyridamole
	1.0	Multiple combined therapy + mPSL + PE
	1.3	ALD + Sairei-to
	3.0	Sairei-to
	9.2	ACEI

findings, we diagnosed this patient as having atypical MPGN, because these pathological findings do not satisfy any other criteria of glomerulonephritis. Treatment with 3 mg/kg/day of dipyridamole was started after the renal biopsy, and proteinuria had disappeared 3 months after the onset. However, the development of severe proteinuria and macrohematuria was triggered by a common cold 11 months after the onset. A second biopsy was performed 10 months after the first and showed a mild-to-moderate increase in mesangial cell proliferation and cellular or cellulofibrous crescents in 20 of 22 glomeruli (90.9%). The patient was diagnosed with acute exacerbation of atypical MPGN and treated with multiple combined therapy consisting of prednisolone, cyclophosphamide, heparin/warfarin and dipyridamole. In addition, he underwent intravenous methylprednisolone (mPSL) pulse therapy and plasma exchange therapy. Proteinuria gradually decreased, and a third biopsy performed 3 months after the start of the multiple combined therapy showed focal mesangial cell proliferation and fibrous crescents in 6 of 20 glomeruli (30.0%). Immunofluorescent studies showed positive deposits of C3, and electron microscopic examination mesangial, subepithelial electron-dense deposits. The multiple combined therapy was continued for 12 weeks and replaced with 30 mg of alternate-day prednisolone. Alternate-day prednisolone was continued for 24 months, then discontinued. At the most recent follow-up (15 years and 1 month after the onset), he had only 300 mg/day of urinary protein with ACE inhibitor treatment. His renal function (serum creatinine 0.8 mg/dl) and blood pressure continue to be normal, and he has not developed any adverse effects attributable to his medications.

Follow-up biopsy

Three patients underwent follow-up biopsy (patients 2, 5 and 7). Patient 2 was a 9-year-old girl who presented with asymptomatic proteinuria and microscopic hematuria detected by a school urinary screening program. Her serum C3 level was normal. The first renal biopsy performed 8 months after the detection of the urinary abnormalities led to a diagnosis of atypical MPGN (Tables 2 and 3). Treatment with Sairei-to was started after the renal biopsy and in combination with ACE inhibitor 8 months later. A second renal biopsy was performed 4 years after the first. Light microscopy showed minor glomerular abnormalities, no C3 deposits were detected in the capillary walls or mesangial areas. Electron microscopic examination could not be performed. Urinalysis findings were normal at the last follow-up 5 years after the onset. Patient 5 was a 14-year-old girl who presented with microscopic hematuria detected by a school urinary screening program. She developed proteinuria with a serum C3 level of 8 mg/dl 1 year and 9 months after the detection of hematuria. The first renal biopsy, performed 2 years and 2 months after the detection of the urinary abnormalities, led to a diagnosis of atypical MPGN (Tables 2 and 3), and treatment with Sairei-to was started after the renal biopsy. Proteinuria and hematuria contin-

Table 5 Outcome. *H* hematuria; *P* proteinuria; C3 normal range: 65–135 mg/dl

Patient no.	Urinalysis at last follow-up	Period of low C3 (years)	C3 at last follow-up (mg/dl)	Follow-up period (years)
1	Normal	1.6	72	15.3
2	Normal	0	125	5.2
3	H	–	32	3.2
4	Normal	0.6	76	9.7
5	Normal	2.2	88	9.9
6	Normal	1.3	82	11.3
7	P (+)	0.3	70	15.1

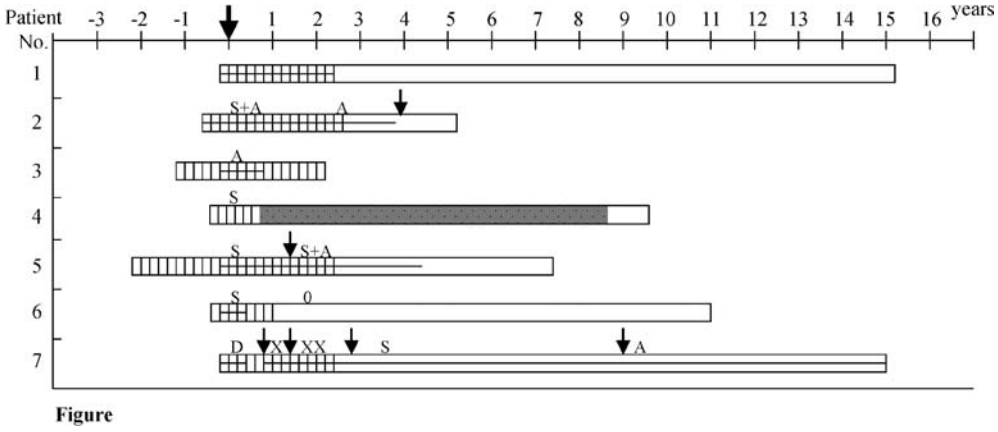

Fig. 1 Patient course and treatment (*open bar* with *vertical line*: hematuria; *open bar* with *horizontal line*: proteinuria; *open bar*: normal urinalysis; *gray bar*: no medical record). *Zero time* indicates the first renal biopsy (*large arrow*). *Arrow* indicates renal biopsy. *S* Sairei-to; *A* angiotensin-converting enzyme inhibitor; *D* dipyridamole; *X* multiple combined therapy with methylprednisolone and plasma exchange; *XX* alternate-day prednisolone; *0* discontinuation of medication

ued, and a second renal biopsy was performed 1 year and 3 months after the first. Light microscopy showed focal mesangial cell proliferation and segmental double contour. The results of electron microscopic examination and immunofluorescent studies were almost similar to those of the first biopsy, and treatment with ACE inhibitor was added after the second biopsy. Hypocomplementemia continued for 2 years and 2 months, and proteinuria continued for 4 years and 5 months, but urinalysis findings were normal at the last follow-up.

Outcome

The mean follow-up period was 10.0±1.7 (mean±SE) years (Table 5 and Fig. 1). Urinalysis findings at the last follow-up were normal for five patients, proteinuria was still present in one patient (patient 7) and hematuria also persisted in one patient (patient 3). At the most recent follow-up, all patients showed renal function within the normal range, as well as normal serum albumin, blood urea nitrogen and creatinine levels. Serum C3 levels had returned to normal in five of six patients, but in one (patient 3) hypocomplementemia persisted until the last follow-up.

Discussion

This report describes the long-term clinical course of seven children with atypical MPGN, all but one of whom were treated without corticosteroids. One patient (patient 7) who was treated with corticosteroids developed acute crescenteric glomerulonephritis triggered by a common cold. He presented with macrohematuria with severe proteinuria, but proteinuria immediately decreased at the first renal biopsy. His pathological findings at the first biopsy were similar to that of others, although mesangial cell proliferation was mild under LM, and subendothelial deposits were not observed under EM. We diagnosed him as having atypical MPGN, because his pathological findings did not satisfy any other criteria of glomerulonephritis. However, the reason he developed acute crescenteric glomerulonephritis is not clear. The urinary abnormalities of five patients had disappeared, one (patient 3) showed signs of hematuria and one (patient 7) had proteinuria at the last follow-up. None of the patients progressed to ESRF. The prognosis of our seven patients with atypical MPGN was good.

MPGN is a progressive primary glomerulonephritis characterized morphologically by endocapillary proliferation, increased mesangial matrix and duplication and/or thickening of the glomerular basement membrane. In many cases it leads to ESRF after several years [3, 8, 24].

In 1973, Habib [1] listed 4 patients with focal MPGN among 782 with biopsy evidence of glomerulonephritis, and subsequently, with her colleagues, has referred to this form in a number of reports on the same patient population [25, 26]. In 1982, Strife et al. [2] reported they had identified 6 patients with focal segmental MPGN among 61 children with MPGN. All but one of their patients were treated with prednisolone using an alternate-day regimen, and their urinary abnormalities generally diminished or disappeared during the 2 to 16 years of follow-up. They concluded that focal segmental MPGN appears to be an early manifestation of typical MPGN.

In Japan, the Ministry of Education began its school urinary screening programs aimed at the early detection of insidious renal diseases in 1974 [27]. MPGN has been diagnosed in an increasing number of asymptomatic school children identified in urinary screening programs [15], and several authors have reported on recent findings of atypical MPGN.

Hattori et al. [5] reported eight children with MPGN whose renal biopsies showed involvement of only some glomeruli and glomerular capillaries with a segmental distribution, i.e., focal MPGN. Five children were treated with corticosteroids and had a good prognosis. However, two patients who were not adequately treated with corticosteroids continued to show signs of hematuria and proteinuria, and their segmental lesions progressed to typical MPGN. The authors concluded that the various subtypes of MPGN could undergo interconversion depending upon changes in the patient's condition and recommended that patients with focal MPGN should be treated with corticosteroids.

Iitaka et al. [6] reported eight children with focal segmental MPGN, all but one of whom received alternate-day prednisolone therapy. Urinalysis findings became normal for six patients, while two continued to have proteinuria with or without hematuria, while MPGN lesions and mesangial proliferation improved. Since focal segmental MPGN seemed to have an excellent prognosis, the authors suggested that the duration and dosage of alternate-day prednisolone should be further reduced.

The severity of the clinical status of our seven patients with atypical MPGN was similar to that of Iitaka et al. [6], although the percentage of glomeruli with double-contoured appearance was less than that of their patients. However, only one of our patients was treated with corticosteroids, and none showed a progression of atypical MPGN lesions to typical MPGN.

According to some reports, clinical and histological improvement followed steroid therapy with immunosuppressive and anti-inflammatory agents, anticoagulants or antiplatelet agents [7, 8, 28]. Data from some, though not all, clinical trials suggest that the alternate-day steroid therapy is the most thoroughly investigated regimen for children with typical MPGN [7, 8, 9, 10, 11] and is currently used as the standard therapy for children with atypical MPGN [2, 5, 6, 12].

However, the use of alternate-day steroid medication is not without complications. Especially, the risk of growth retardation is a serious problem for growing children, so that the necessity of steroid medication for children with atypical MPGN merits a careful reevaluation.

Recently, the anti-proteinuric and renoprotective effects on various renal diseases of the blockade of angiotensin II action with an angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor blockers (ARB) have been reported [29, 30, 31, 32]. Butani [33] describes the case of a 14-year-old girl with idiopathic type I MPGN accompanied by nephrotic-range proteinuria (15 g/day). She was treated with an ACEI (lisinopril) and an ARB (valsartan), and 16 months after the diagnosis she registered only 200 mg/day of urinary protein. Butani concluded that these agents, which have traditionally not been considered immunosuppressive, have definite immunomodulating effects and may provide a safer alternative to medications such as corticosteroids.

For the study reported here, we treated five of seven atypical MPGN patients with ACEI and/or the Chinese herbal medicine Sairei-to, with all of them showing an excellent prognosis.

In conclusion, our results demonstrate that the prognosis of atypical MPGN was good in most patients without corticosteroids, but one developed acute crescenteric glomerulonephritis while being observed and was treated aggressively with corticosteroids. The reason for this course is not clear. However, all of our children with atypical MPGN did well at the last follow-up. We therefore recommend that the current common practice of treating all children with atypical MPGN with corticosteroids should be re-examined. Further studies, including more patients and longer follow-up periods, are needed to conclusively determine whether steroid therapy can be omitted for atypical MPGN.

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