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BRIEF REPORT

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Plasmapheresis therapy for rapidly progressive Henoch-Schönlein nephritis

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Abstract Six Japanese children with rapidly progressive Henoch-Schönlein purpura nephritis (HSPN) received multiple drug therapy combined with plasmapheresis (PP). After five courses of PP, multiple drug therapy, including methylprednisolone and urokinase pulse therapy, oral prednisolone, cyclophophamide, dipyridamole, and warfarin was given. At presentation, urine protein excretion and histological indices of the mean activity and chronicity were 245±101 mg/m^2 per hour, 6.6±1.2, and 1.5±1.3, respectively. After 6 months of therapy, urinary protein excretion had decreased significantly (P<0.001). The activity index decreased significantly at the second renal biopsy performed at a mean interval of 4.3 months after the first (2.8±1.4, P<0.05), while the chronicity index did not change. At the most recent observation, all showed clinical improvement. Two patients had normal urine, three had proteinuria of <20 mg/m^2 per hour, one had proteinuria of >20 mg/m^2 per hour, and none had renal insufficiency. Although this case series is without controls, our treatment protocol may be of benefit to children with rapidly progressive HSPN.

Keywords Henoch-Schönlein purpura nephritis · Plasmapheresis · Rapidly progressive glomerulonephritis · Multiple drug therapy · Prognosis

Introduction

The incidence of renal involvement in Henoch-Schönlein purpura (HSP) varies between 20% and 80%. Most children with HSPN present only with hematuria and/or low-grade proteinuria, or both, and have a good chance of recovery. However, patients with massive proteinuria at onset frequently have a progressive course [1, 2]. In specialized centers, the proportion of children with HSPN who progress to renal failure or end-stage renal disease varies from 12% to 19% [1, 2, 3, 4]. The prognosis of patients with HSPN presenting as rapidly progressive glomerulonephritis (RPGN) was poor [2]. This poor outcome has led to the use of multiple treatment regimens. Corticosteroids, both alone and with cytotoxic agents, anticoagulants and antiplatelet agents, plasmapheresis (PP), and intravenous methylprednisolone, in different combinations, have all been employed [3, 4, 5, 6]. We recently reported that methylprednisolone and urokinase (UK) pulse therapy was effective in HSPN patients with at least type IIIb disease [7]. However, there are few reports of PP and multiple drug therapy for children with rapidly progressive HSPN. The aim of this study was to evaluate the clinical and laboratory effects of multiple drug therapy combined with PP in rapidly progressive HSPN.

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Patients and methods

Patients

We studied six patients who had been diagnosed with rapidly progressive HSPN at the Department of Pediatrics, Fukushima Medical University School of Medicine between 1995 and 2002. Entry criteria included: (1) the major manifestations of the illness consisted of a purpuric rash and abdominal pain without thrombocytopenia; additional features including arthritis and nephritis were accepted as consistent with the diagnosis; (2) no previous treatment with corticosteroids or immunosuppressive drugs. The clinical features, laboratory data, and pathological findings were retrospectively investigated between, before, and after therapy.

Definitions

RPGN was characterized histologically by the presence of extensive crescent formation (over 60%) in the renal biopsy and clinically by a sudden progressive decline in renal function [50% or more in glomerular filtration rate (GFR) within 6 weeks] together with a nephritic urine sediment (dysmorphic hematuria, cylindru-

ria) and nephrotic-range proteinuria (>40 mg/m^2 per hour). GFR was determined as a 24-h creatinine clearance (24-h C_{Cr}).

Treatment protocol

Following a diagnostic renal biopsy, PP was performed by plasma separation using either centrifugation (IBM Model 2997 continuous blood cell separator, COBE Laboratories, Tokyo, Japan) or membrane filtration (Asahi Plasmaflo System, Asahi Medical, Tokyo, Japan), with a volume of 50 ml/kg body weight of plasma exchanged at each session. A 5% human albumin solution was used as a substitution solution. The PP regimen consisted of five treatments for 2 weeks. In the 1st week, plasmapheresis was performed on alternate days for 3 days, and in the 2nd week it was performed on alternate days for 2 days.

After PP, multiple drug therapy was performed. This was a combination of pulse methylprednisolone at 30 mg/kg per day i.v. bolus (maximum 1 g) for 3 consecutive days and of pulse UK at 5,000 U/kg per day i.v. bolus (maximum 180,000 U) for 7 consecutive days, followed by daily oral prednisolone (1 mg/kg per day) for 6 months, along with dipyridamole (5 mg/kg per day) and warfarin. Warfarin was given orally in a single morning dose of 1 mg (less 7 years of age) or 2 mg (more than 7 years of age) to maintain the thrombotest at 30%–50%. In addition, cyclophosphamide (2.5 mg/kg per day) was administered for 12 weeks. Cyclophosphamide was given orally in a single morning dose to maintain the pseudocholinesterase (ChE) level at more than half of the pre-therapy ChE or lymphocyte counts at more than 1,500/μl, or both. The corticosteroid dose was subsequently reduced over 3 months according to individual improvement in 24-h C_{Cr}, urinary sediment, and urinary protein.

Pathology

All patients received a second biopsy at a mean interval of 4.3 months in order to assess the efficacy of the therapy. The mean number of glomeruli found in the first and second biopsy specimens was 17.0±5.2 (11–24) and 21.6±9.3 (12–32), respectively. The specimens were assessed by light microscopy and immunofluorescence.

The glomerular changes were graded according to the classification devised by the pathologists of the International Society of Kidney Disease in Children [8]. To compare the biopsies, a histological scoring system was modified to evaluate acute and chronic changes [9]. Acute changes included mesangial proliferation (grade 0–3, 0=normal, 1=slight, 2=moderate, 3=severe), segmental necrosis with cellular crescent formation (scored according to the percentage of glomeruli involved, 0=0%, 1=1–20%, 2=20–50%, 3=>50%), and interstitial edema with mononuclear cell infiltration (0–3). The acute index (AI) is the sum of these scores including mesangial proliferation, cellular crescent formation, and interstitial edema. Chronic renal injury was estimated by determining the number of glomeruli demonstrating fibrous crescents and segmental or global sclerosis. Each abnormality was scored 0–3 according to the number of glomeruli involved, as for acute crescent formation. In addition, the combination of tubular atrophy and interstitial fibrosis was graded 0–3. The chronicity index (CI) is the sum of these scores, including glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Scoring was performed in a blind fashion.

Statistics

Data are expressed as mean values±SD and were analyzed by statistical analysis (Stat View, Abacus Concepts, Berkeley, Calif., USA). Differences in laboratory findings were assessed by Student's *t*-test. P<0.05 was considered significant.

Results

The clinical characteristics of the six patients are shown in Table 1 and included oliguria in three patients, hypertension in five patients, and edema and macroscopic hematuria in all patients. The age at onset and duration of follow-up were 9.7±2.2 years and 54.7±17.3 months, respectively. The male/female ratio was 1:5. Nephrotic-range proteinuria was present in all patients and ranged from 139 to 416 mg/m^2 per hour (mean 245±101). All patients had a decreased GFR (<60 ml/min per 1.73 m^2, range 24–54, mean 42±11). One patient (no. 1) required peritoneal dialysis for a period of 10 days during the acute stage. Histological indices of the mean AI and CI were 6.7±1.2 and 2.0±1.1, respectively. The percentage of glomeruli showing crescents was 76±11%. After 6 months of therapy, urinary protein excretion had decreased significantly (P<0.001) to 27±29 mg/m^2 per hour. The second renal biopsy showed significant decreases in the AI and percentage of glomeruli showing crescents (2.2±0.8, 11±7% P<0.01, respectively). The CI did not change compared with the first biopsy.

At the most recent follow-up, the mean urinary protein excretion was 11±10 mg/m^2 per hour and the 24-h C_{Cr} had returned to normal in all patients. Two patients had normal urinalysis, three had proteinuria of <20 mg/m^2 per hour, one had proteinuria of >20 mg/m^2 per hour, and none had renal insufficiency.

Three patients showed cushingoid changes and one developed mild hypertension, which was well controlled by nifedipine. One patient developed leukopenia and discontinued the cyclophosphamide for 12 weeks. Most of the side effects were mild and well controlled.

Discussion

HSP is an IgA-mediated immune complex vasculitis that affects predominantly the skin, joints, gastrointestinal tract, and kidneys. It occurs most frequently in childhood, and its prognosis is mainly predicted by the severity of renal involvement.

The mechanisms involved in the pathogenesis of HSPN are still poorly understood, but several lines of evidence suggest that immunological factors, including immune complexes, may be involved. The presence of IgA and IgM immune complexes in the glomerular mesangium of patients with HSPN strongly suggests an important role for these in the pathogenesis of the renal damage [1, 2, 3]. In particular, these immune complexes were particularly marked in rapidly progressive HSPN. Therefore, it is important to implement sufficient therapy for patients with HSPN presenting as RPGN.

Gianviti et al. [10] showed that plasma exchange associated with immunosuppressive treatment could be of benefit in cases of idiopathic RPGN or vasculitis. Hattori et al. [6] reported that PP as sole therapy is effective in improving the prognosis of patients with rapidly progressive HSPN. However, there have been few reports of

Table 1 Data on six children with rapidly progressive Henoch-Schönlein purpura nephritis (*Mac* macroscopic hematuria, *Mic* microscopic hematuria, *GFR* glomerular filtration rate, *F* first biopsy, *S* second biopsy, *AI* acute index, *CI* chronicity index, *ISKDC* International Study of Kidney Disease in Children)

Patient no.	Age (years, sex)	Signs and symptoms			Laboratory findings				Pathological findings							The time from onset to treatment	Interval of biopsy	Follow-up
					Urinary protein (mg/m^2 per hour)		Hematuria		GFR (ml/min per 1.73 m^2)		AI		CI		ISKDC classification			
		Edema	Oliguria	Hyper-tension	Onset	The latest observation	Onset	The latest observation	Onset	The latest observation	F	S	F	S	F	S	(months)	(months)	(months)
1	8/F	+	+	+	416	29	Mac	Mic	24	62	6	3	4	4	V	III	18	6	84
2	10/F	+	-	+	139	6	Mac	-	52	91	5	2	2	3	IV	III	24	4	66
3	8/M	+	-	-	149	0	Mac	Mic	54	94	8	2	1	1	IV	III	30	3	52
4	14/F	+	+	+	278	10	Mac	Mic	46	102	6	3	2	3	V	III	21	4	41
5	10/F	+	-	+	226	5	Mac	Mic	37	88	7	1	1	1	IV	II	34	5	38
6	8/F	+	+	+	260	17	Mac	Mic	39	98	8	4	2	3	IV	III	30	4	48

multiple drug therapy combined with PP for children. Our study suggested that multiple drug therapy combined with PP significantly reduced urinary protein excretion and prevented any increase in crescentic and sclerosed glomeruli in severe HSPN with RPGN. Moreover, at the latest follow-up, there were no patients with renal insufficiency.

The mechanisms by which PP benefits patients with severe HSPN remain largely obscure. However, immunological findings in experimental and clinical HSPN suggest that PP removes IgA-containing immune complexes or aggregates, or proinflammatory mediators, including cytokines and complement, reduces fibrinogen or other coagulation factors, and possibly leads to desaturation of the mononuclear phagocyte system [4].

In contrast, it has been suggested that activation of intraglomerular blood coagulation exacerbates HSPN [11]. Administration of steroids may lead to a hypercoagulable state and the formation of thrombi. Moreover, Miura et al. [12] reported that the deposition of fibrinogen and/or α_2-plasmin inhibitor in glomeruli exacerbates glomerulonephritis. Since an intraglomerular hypercoagulable state was histopathologically related to renal injury, it was considered that fibrinolytic therapy, including UK, might be a beneficial approach to preserve renal function in patients with IgA nephritis [12]. We found that UK pulse therapy improved the prognosis of HSPN patients with at least grade III severity [7]. The rationale for anticoagulation drugs was as follows: (1) there was stronger defibrinating activity with UK than with anticoagulant drugs; (2) specific accumulation of UK was observed in the kidney and liver despite a very short turnover rate.

The rationale for using our treatment in severe HSPN is that PP removes these mediators and corticosteroids and immunosuppressive agents reduce IgA production and minimize the abnormal immune response and inflammatory events. In addition, warfarin and dipyridamole are used to inhibit the mediators of glomerular damage.

Although this case series is without controls, our treatment protocol may be of benefit to children with rapidly progressive HSPN. However, it is difficult to draw any conclusions from this study, because few patients were examined and the observation period was short. Hence, further studies in children with rapidly progressive HSPN are needed.

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