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Multiple combined therapy for severe Henoch-Schönlein nephritis in children

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Abstract. From 1980 through 1992, 14 children with Henoch-Schönlein nephritis (HSN) showing severe glomerular changes (grade IV or V) were given a multiple combined therapy with prednisolone, cyclophosphamide, heparin/warfarin, and dipyridamole, and were followed for 7.5 ± 0.9 years. The period between the onset of nephritis and the start of therapy was 0.8 ± 0.4 years. Ten patients underwent follow-up biopsy after therapy. The percentage of glomeruli having crescents/segmental lesions was significantly reduced after therapy ($70\% \pm 5\%$ vs. $42\% \pm 7\%$, $P < 0.01$), due mainly to the resolution of crescents ($51\% \pm 8\%$ vs. $13\% \pm 5\%$, $P < 0.01$). Thus, histological grade was significantly improved (5 grade IV and 5 grade V vs. 7 grade III and 3 grade IV, $P < 0.01$). After an average follow-up period of 7.5 years, 9 patients showed normal urine and renal function, 4 showed minor urinary abnormalities, and 1 heavy proteinuria. No patient developed chronic renal insufficiency. These findings suggest that the multiple combined therapy could be effective for histologically severe HSN, although a prospective controlled study should be performed.

Key words: Henoch-Schönlein nephritis – Multiple combined therapy – Histological effects – Prognosis

Introduction

Henoch-Schönlein purpura syndrome occurs predominantly during childhood and is frequently accompanied by renal involvement, Henoch-Schönlein nephritis (HSN). While most children with HSN recover completely without any treatment, a small proportion develop chronic renal failure [1, 2]. HSN is a significant cause of childhood chronic renal failure, accounting for 16% of all children entering dialysis programs in Japan [3]. The prognosis of HSN correlates well with early glomerular changes [3]. Therefore, patients with severe glomerular changes should be treated effectively at an early stage. Here we report the clinical and histological effects of a multiple combined therapy consisting of prednisolone, cyclophosphamide, heparin/warfarin, and dipyridamole for children with histologically severe HSN.

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Patients and methods

Patients and laboratory findings. HSN was diagnosed when hematuria was associated with a characteristic purpuric rash and either abdominal or joint pain, or both [4]. Renal biopsy was performed in children with acute nephritic and/or nephrotic syndrome and in children with persistent proteinuria (≥ 1 g/day per m^2 body surface area for > 1 month or $0.5-1$ g/day per m^2 for > 3 months).

The clinical and laboratory findings in the patients were obtained from the medical records after examination of biopsy specimens. Hematuria was defined as an erythrocyte excretion of $\geq 10/mm^3$ of uncentrifuged urine or 5 per high-power field of centrifuged urine. Acute nephritic syndrome was defined as hematuria associated with hypertension and/or glomerular filtration rate (GFR) of < 60 ml/min per 1.73 m^2. Nephrotic syndrome was defined by heavy proteinuria and hypoalbuminemia of ≤ 25 g/l. Heavy proteinuria was defined as a urinary protein excretion of ≥ 1.0 g/day per m^2 body surface area. Hypertension was diagnosed when the diastolic pressure was persistently > 90 mmHg. GFR was determined by creatinine clearance, the lower limit of the normal range in our laboratory being 80 ml/min per 1.73 m^2. Renal insufficiency was defined by decreased GFR of < 60 ml/min per 1.73 m^2. The clinical status of each patient at follow-up was then classified according to the scheme originally devised by Meadow et al. [5] and modified by Counahan et al. [6]. State A – normal: results of physical examination (including blood pressure), urinalysis, and renal function were all normal; state B – minor urinary abnormalities: normal results of physical examination and renal function, with micro- or macroscopic hematuria or proteinuria of < 1 g/day per m^2, or both; state C – active renal disease: proteinuria of ≥ 1 g/day per m^2 or hypertension, or both with GFR of ≥ 60 ml/min per 1.73 m^2; state D – renal insufficiency: active renal disease with GFR of < 60 ml/min per 1.73 m^2 (including dialysis/transplantation) or death.

Table 1. Clinical data of 14 patients with severe Henoch-Schönlein nephritis treated with a multiple combined therapy

Patient no.	Age (years)/sex	Initial presentation	Clinical status at completion of therapy	Follow-up after therapy (years)	Clinical status at the latest observation
1	11.7/M	Nephritic and nephrotic	B	13.3	B
2	5.1/M	Nephritic	A	12.5	A
3	6.4/F	Nephritic and nephrotic	A	12.1	A
4	7.1/F	Hp and h	B	10.4	A
5	6.9/F	Hp and h	B	9.9	A
6	9.3/F	Sp and h	B	7.0	B
7	5.3/M	Nephritic	B	5.2	A
8[a]	5.7/M	Hp and h	B	5.2	A
9	7.1/F	Hp and h	B	5.0	A
10	13.8/F	Hp and h	B	4.9	B
11[a]	17.5/M	Hp and h	B	4.8	C
12	5.0/F	Nephrotic	C	4.7	A
13[a]	6.4/F	Hp and h	B	4.4	B
14	6.0/F	Nephritic and nephrotic	B	3.4	A

Nephritic, Acute nephritic syndrome; Nephrotic, nephrotic syndrome; Hp and h, heavy proteinuria and hematuria; Sp and h, slight proteinuria and hematuria

[a] These patients initially showed glomerular change of International Study of Kidney Disease in Children (ISKDC) grade II or III, but had shown progression to grade IV or V at the time of second or third biopsy, and were given the therapy

Table 2. Histological data of 14 patients with severe Henoch-Schönlein nephritis treated with a multiple combined therapy

	Pre therapy						Post therapy					
Patient no.	Cre+Seg lesions (%)	ISKDC grade	Cre (%)	Nature of Cre	Global/Seg sclerosis (%)	Ad (%)	Cre+Seg lesions (%)	ISKDC grade	Cre (%)	Nature of Cre	Global/Seg sclerosis (%)	Ad (%)
1	94	V	94	FC	0/0	0	62	IV	26	F	10/16	10
2	54	IV	46	FC	0/4	4	–	–	–	–	–	–
3	82	V	18	FC	0/0	64	–	–	–	–	–	–
4	54	IV	46	C	0/4	4	27	III	0	–	0/20	7
5	78	IV	23	FC	11/11	33	44	III	6	F	6/0	32
6	52	IV	32	FC	0/0	20	36	III	18	F	0/4	14
7	51	IV	49	FC	0/0	2	17	III	10	F	0/3	4
8	54	IV	24	F	2/2	24	44	III	9	F	14/3	17
9	82	V	82	FC	0/0	0	–	–	–	–	–	–
10	83	V	75	FC	0/0	8	–	–	–	–	–	–
11	88	V	75	FC	13/0	0	36	III	9	F	9/9	9
12	63	IV	50	FC	13/0	0	68	IV	47	F	5/0	16
13	83	V	33	FC	0/17	33	15	III	0	–	0/0	15
14	86	V	86	FC	0/0	0	75	IV	0	–	33/9	33

Cre, Crescents; Seg, segmental; Ad, adhesion; C, cellular; FC, fibrocellular, F, fibrous

The glomerular changes were graded according to the classification devised by the pathologists of the International Study of Kidney Disease in Children, as follows: I, minor glomerular abnormalities; II, pure mesangial proliferation; III, minor glomerular abnormalities or mesangial proliferation, with crescents/segmental lesions (sclerosis, adhesion, thrombosis, necrosis) in $<50\%$ glomeruli; IV, same as III but with crescents/segmental lesions in 50%–75% glomeruli; V, same as III but with crescents/segmental lesions in $>75\%$ glomeruli; VI, membranoproliferative-like lesions.

From 1980 through 1992, 14 children (5 boys, 9 girls) were diagnosed as having grade IV or V HSN, received multiple combined therapy, and were followed for more than 3 years. Informed consent was obtained from all the parents/guardians of each child. The mean age ($\pm$SE) at onset was 8.1 ± 1.0 years (range 5.0–17.5 years) and the mean duration of follow-up after therapy was 7.5 ± 0.9 years (range 3.4–13.3 years). The period between the onset of nephritis and the start of therapy was 0.8 ± 0.4 years (range 19 days to 6.0 years). In 11 patients, the treatment was started within 6 months of disease onset.

Multiple combined therapy regimen. The therapeutic protocol for the multiple combined therapy was as follows. Patients were treated with 2 mg/kg per day prednisolone, given in three divided doses (up to a maximum of 80 mg/day) for the first 4 weeks, followed by prednisolone at 2 mg/kg given as a single dose every other morning for 8 weeks, after which the dosage was decreased by 0.5 mg/kg every 2 weeks. Cyclophosphamide was given as a single dose of 2 mg/kg per day each morning for 8 weeks. When leukopenia ($<3{,}000/\mu l$) was evident, cyclophosphamide was transiently discontinued until the number of leukocytes normalized. Heparin was given intravenously (adjusted to maintain activated partial thromboplastin time between 60 and 80 s) for the first 4 weeks, followed by warfarin for 4 weeks. Warfarin was started at 1 mg/day, given as a single dose each morning. The dose of warfarin was then adjusted to give a thrombo test result of 20%–50%. Dipyridamole was started at 3 mg/kg per day given in three divided doses, then the dose of dipyridamole was increased to 6 mg/kg per day (up to a maximum of 300 mg/day), and maintained for 8 weeks if the patient reported no headaches.

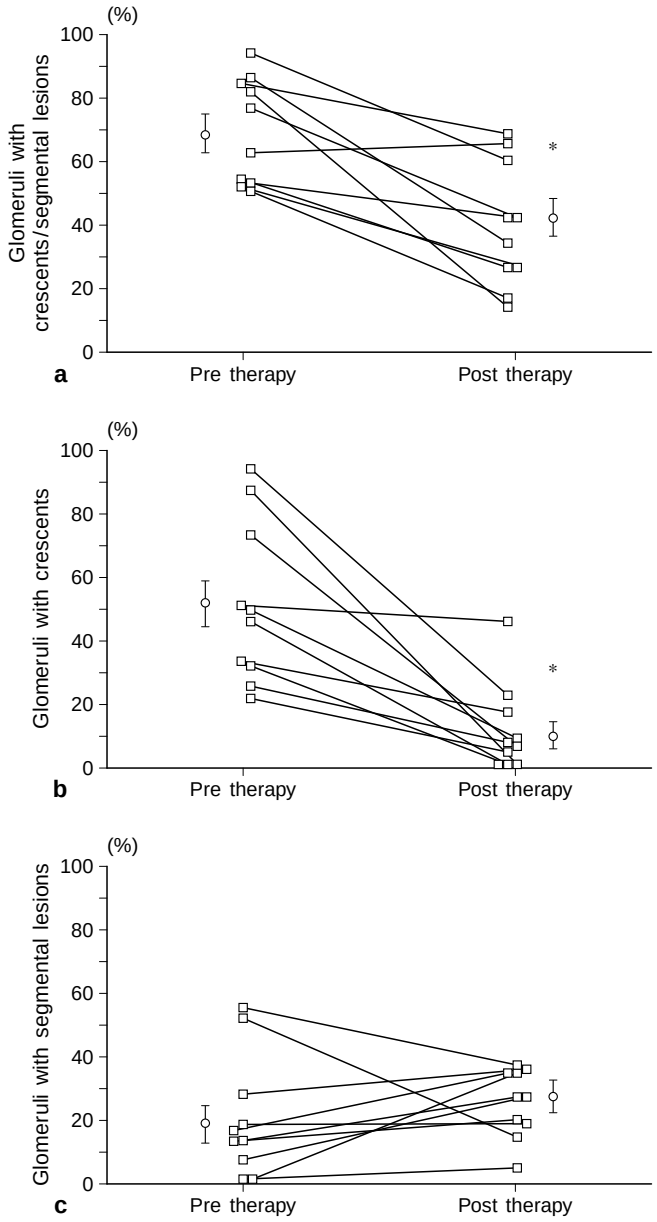

Fig. 1. Glomerular changes before and after the multiple combined therapy: **a** percentage of glomeruli with crescents/segmental lesions; **b** percentage of glomeruli with crescents; **c** percentage of glomeruli with segmental lesions. *$P < 0.01$

Statistical analysis was performed on a Macintosh computer with a software package for statistical analysis (Stat View, Abacus Concepts, Berkeley, Calif., USA). Differences between biopsy findings before and after the therapy were assessed by Wilcoxon signed rank test. The level of significance was a two-tailed P value of < 0.05.

Results

Patients' characteristics

The main initial presentations recorded within 3 months of onset were as follows: 1 patient had slight proteinuria ($\leq$1.0 g/m^2 per day) and hematuria, 7 had heavy proteinuria ($\geq$1.0 g/m^2 per day) and hematuria, 1 had nephrotic syndrome, 2 had acute nephritic syndrome, and 3 had acute nephritic and nephrotic syndrome (Table 1).

The glomerular changes evident at initial biopsy were as follows: grade II in 1 patient, grade III in 2, grade IV in 5, and grade V in 6. Eleven patients showing grade IV or V were treated immediately after the initial biopsy. Patient no. 8 initially showed grade III, and had been treated with dipyridamole. However, he showed persistent heavy proteinuria for a further 6 months. He then underwent a second biopsy, which showed progression to grade IV, and was therefore given multiple combined therapy. Patient no. 11 initially showed grade II, and had been treated with dipyridamole. His urinary findings improved to minor urinary abnormalities within several months. However, 11 months after onset, he had recurrent heavy proteinuria with purpura, and he underwent a second biopsy which showed grade V. Multiple combined therapy was therefore instituted. Patient no. 13 initially showed grade III, and had been treated with prednisolone and dipyridamole for 1 year in another hospital. Her clinical and histological findings improved to minor urinary abnormalities and grade II, respectively, at the time of the second biopsy (1.5 years after onset). However, 6 years after onset, her heavy proteinuria recurred with purpura. A third biopsy showed grade V, and therefore multiple combined therapy was started. Thus, 6 patients showed grade IV and 8 showed grade V just before therapy. Cellular or fibrocellular crescents were predominant in 13 patients, whereas fibrous crescents were predominant in only 1 (no. 8) (Table 2).

Outcome

Clinical findings (Table 1). At the time of completion of therapy, 2 patients showed normal urinalysis and renal function (state A), 11 showed minor urinary abnormalities (state B), and 1 showed heavy proteinuria (state C). No patient showed renal insufficiency (state D).

At the latest observation (7.5 ± 0.9 years after therapy), 9 patients were in state A, 4 were in state B, and 1 was in state C. No patient was in state D. One patient with state C at the latest observation (no. 11) showed an improvement of histological grade from V to III, and of clinical status from active renal disease (state C) to minor urinary abnormalities (state B) just after the therapy. However, his urinary findings deteriorated again after recurrence of purpura at the time of an upper respiratory tract infection, 4 years later.

Follow-up biopsy (Table 2). Ten patients underwent follow-up biopsy 9.9 ± 3.1 months (range 3–24 months) after the pre-therapy biopsy. The percentage of glomeruli having crescents/segmental lesions was significantly reduced after the therapy: pre therapy, $70\% \pm 5\%$; post therapy, $42\% \pm 7\%$ ($P < 0.01$, Fig. 1a). This was due mainly to the resolution of crescents: pre therapy, $51\% \pm 8\%$, post therapy, $13\% \pm 5\%$ ($P < 0.01$, Fig. 1b). The crescents were small and fibrous in all post-therapy biopsy specimens. The percentage of glomeruli having segmental lesions was not changed after therapy: pre therapy, $19\% \pm 6\%$; post therapy, $29\% \pm 5\%$ ($P > 0.05$, Fig. 1c). Thus, the histological grade

was significantly improved after therapy: pre therapy, 5 grade IV and 5 grade V; post therapy, 7 grade III and 3 grade IV ($P < 0.01$).

Side effects of therapy

Two patients developed mild glaucoma, 2 had more than 10% body weight gain, and 2 developed infection. One of the latter developed suspected bacterial infection with high-grade fever and an elevated level of C-reactive protein. However, she recovered after treatment with antibiotics, transient discontinuation of cyclophosphamide, and reduction of prednisolone. The other patient with infection developed otitis media, which was resolved by treatment with antibiotics. One patient developed hypertension, which was well controlled by treatment with furosemide and captopril. One patient developed urticaria. The doses of anticoagulants used in the present study did not result in severe bleeding tendency. In summary, most of the side effects were mild and well controlled, and all were reversible.

Discussion

Although the value of corticosteroids in managing severe abdominal pain in Henoch-Schönlein purpura is well documented, it has been reported that there is no specific treatment of unquestionable benefit for nephritis. In fact, several investigators have reported that corticosteroids have no benefit [5–8]. Also, immunosuppressive agents, including azathioprine, cyclophosphamide, and chlorambucil, are not believed to be effective [5–7]. However, an uncontrolled trial of combined steroid, immunosuppressant, and anticoagulant therapy for rapidly progressive crescentic glomerulonephritis of various causes, including HSN, has suggested that deterioration of renal function could be retarded or occasionally halted, provided that the patient was not already severely oliguric [9]. Therefore, the present study was designed to assess the effects of multiple combined therapy with prednisolone, cyclophosphamide, heparin/warfarin, and dipyridamole for histologically severe HSN, which is considered to have a poor prognosis.

By means of serial renal biopsy, Niaudet et al. [10] demonstrated a good correlation between the histological changes with time and both the clinical status and outcome of the patients. Patients who improved showed transition of previous crescents to small fibrous adhesions, in addition to a reduced number of affected glomeruli. In contrast, patients with active nephritis usually showed fibrous crescents and segmental sclerosis in similar proportions in the affected glomeruli. In the present study, most of the patients received therapy in the acute phase of nephritis, since cellular or fibrocellular crescents were predominant. Follow-up biopsy revealed that the percentage of glomeruli with crescents was significantly reduced (crescents disappeared in several cases), although the percentage of those with segmental lesions such as sclerosis and adhesion was not changed. Therefore, overall histological grade was significantly improved. These findings indicate that multiple combined therapy for acute-phase severe HSN ameliorates the glomerular changes and probably improves the outcome. One patient in the present study, who showed histological and clinical improvement just after therapy, subsequently showed clinical deterioration with recurrence of purpura. Collectively, the multiple combined therapy appeared to be effective for acute-phase HSN but ineffective for chronic active HSN.

It has been reported that the prognosis of patients with an initial histological grade of IV and V is poor. Counahan et al. [6] reported that 7 of 21 patients (33%) developed chronic renal insufficiency after a mean follow-up period of 9.9 years. In our previous report, 24 patients initially showing grades IV ($n = 12$) and V ($n = 12$) were treated with corticosteroids, including pulse therapy, or immunosuppressants, or both, or received no treatment. Three of 12 grade IV patients (25%) and 9 of 12 grade V patients (75%), thus, 12 of all the patients (50%), developed chronic renal insufficiency after a mean follow-up period of 4.7 years [3]. In the present study, none of 11 patients initially showing grades IV and V, and none of 14 showing grades IV and V just before therapy, developed chronic renal insufficiency after a mean follow-up period of 7.5 years. These findings suggest that multiple combined therapy improves the prognosis of histologically severe HSN, due probably to improvement of acute-phase glomerular changes.

Öner et al. [11] recently reported that triple therapy (steroids, cyclophosphamide, and dipyridamole) may be effective for rapidly progressive HSN [11]. Fibrin deposition within Bowman's space is known to facilitate crescent formation in animal models of crescentic glomerulonephritis [12]. The quadruple therapy approach with steroids, cyclophosphamide, anticoagulants, and dipyridamole was initiated by Kincaid-Smith in the late 1960s. She developed the approach for patients with any severe crescentic/necrotic glomerulonephritis. We therefore used the quadruple therapy, including heparin/warfarin, although the efficacy of these anticoagulants is not clear.

Several investigators, including White [13] expressed misgivings about the side effects of combined therapy, especially anticoagulants and alkylating agents, for the treatment of HSN. However, in the present study, most of the side effects were mild and well controlled, and all were reversible. No patient developed severe bleeding tendency. One patient developed suspected bacterial infection with high-grade fever and an elevated level of C-reactive protein. However, she recovered after treatment with antibiotics, transient discontinuation of cyclophosphamide, and reduction of prednisolone. In addition, she showed normal urinalysis with normal renal function after completion of the therapy, even though the clinical course was rapidly progressive, suggesting that the therapy had been quite effective. In summary, the side effects of the therapy could be managed by careful observation and treatment, although the frequencies of late complications of cyclophosphamide, including bladder cancer and other malignancies, are not known in the present study.

Goldstein et al. [14] have reported that some patients, who were considered to have recovered clinically, with normal blood pressure, urine, and plasma creatinine concentration, showed clinical deterioration at their final as-

sessment more than 19 years later, although it is not clear whether they had had recurrence of purpura. Thus, long-term follow-up is required for patients who appear normal upon follow-up or have minor urinary abnormalities, as well as those with active renal disease.

In conclusion, multiple combined therapy with prednisolone, cyclophosphamide, heparin/warfarin, and dipyridamole could be effective for children with histologically severe HSN, although a prospective controlled trial needs to be performed.

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Literature abstract

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Volume sensitivity of blood pressure in end-stage renal disease

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Background. The influence of interdialysis (ID) volume expansion on the blood pressure (BP) change and on the BP level at the end of the ID time period was studied in 167 chronic haemodialysis patients. Our analysis focused on 120 patients not receiving antihypertensive drugs (untreated group). The remaining 47 patients were receiving antihypertensive medication (treated group).

Methods. The ID weight gain was considered equivalent to the volume gain. In each patient the mean ID BP change (as percent change of initial BP) and the mean ID volume expansion related to the lean body mass (ml.kg^{-1}) were determined from 25 consecutive ID time periods. The individual volume sensitivity of BP was expressed as the BP change divided by the volume expansion. Basal overhydration was estimated as mean ID initial weight minus dry weight.

Results. All patients gained volume during ID time periods and the BP was increased in 91%. The change of mean BP (MBP) was directly correlated with volume expansion ($r = 0.45$, $P < 0.00001$) only in the untreated group. These patients showed a volume sensitivity unrelated with age, serum urea and calcium concentrations and haematocrit. Sensitivity of diastolic BP (DBP), an indicator of the capacity to respond to volume expansion by vasoconstriction (autoregulatory process), exhibited a negative correlation with the initial DBP level ($r = -0.36$, $P < 0.0001$) and with the serum potassium (in women, $r = -0.35$, $P < 0.02$). These factors appeared to counteract the volume-induced DBP response. The MBP levels at the end of ID time periods were independent of volume expansion and basal overhydration. Hypertensive patients showed a higher sensitivity than normotensive patients (0.35 ± 0.2 versus 0.20 ± 0.19% per ml.kg^{-1}, $P < 0.005$). Final MBP showed a positive correlation with initial MBP and, to a smaller extent, with serum urea concentration.

Conclusions. In our study the ID change of BP is partially dependent on volume gain. Volume sensitivity is a measure of the BP responsiveness and is higher in hypertensive patients. Final BP depends on the height of initial BP and other factors accounting for volume sensitivity, whose precise nature remain to be clarified.