



Title	Henoch-schönlein purpura nephritis in childhood: pathogenesis, prognostic factors and treatment
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[Review]

## HENOCH-SCHÖNLEIN PURPURA NEPHRITIS IN CHILDHOOD : PATHOGENESIS, PROGNOSTIC FACTORS AND TREATMENT

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**Abstract :** Henoch-Schönlein purpura (HSP) is a systemic disorder characterized by leukocytoclastic vasculitis involving the capillaries and the deposition of IgA immune complexes. Renal involvement is the principal cause of morbidity and mortality in children with HSP. Thus, it is important to clarify the onset mechanism as well as the prognostic factors of Henoch-Schönlein purpura nephritis (HSPN) and to identify the most appropriate treatment. We herein review the pathogenesis, the prognostic factors and treatment of HSPN. As to the pathogenesis, several studies suggest that galactose-deficient IgA1 (Gd-IgA1) is recognized by anti-glycan antibodies, leading to the formation of circulating immune complexes and their mesangial deposition, thereby inducing renal injury. With regard to the prognostic factors, a number of factors have been suggested including nephrotic syndrome, decreased factor XIII activity, hypertension, severe renal injury, high renal accumulation of activated macrophage, alpha-smooth muscle actin, and high serum myeloid-related protein levels.

For the treatment of severe HSPN, aggressive therapies including multiple drug combination therapy and plasmapheresis have been shown to be effective in ameliorating proteinuria and histological severity. Nevertheless, detailed investigation into the pathogenesis of HSPN and double-blind randomized control studies on children with HSPN are still necessary.

**Key words :** HSPN, Pathogenesis, urokinase pulse therapy, cyclophosphamide, mizoribine

### INTRODUCTION

Henoch-Schönlein purpura (HSP) was first recognized by Heberden in 1801 and first described as an association between purpura and arthritis by Schönlein in 1837. Henoch added descriptions of gastrointestinal involvement in 1874 and renal involvement in 1899. HSP is a small vessel vasculitis, the major manifestations of which include arthritis, nonthrombocytopenic purpura, abdominal pain, and renal disease. HSP is one of the most common vasculitides of childhood and is considered to be self-limiting. One manifestation of HSP that can result in lifelong problems is renal involvement<sup>1,2)</sup>. Approximately 40% of pediatric patients develop nephritis within 4 to 6 weeks of the initial

presentation. A majority of children with HSPN present with only hematuria and/or low-grade proteinuria, or both, and have a good chance of recovery. However, patients with massive proteinuria at onset frequently show a progressive course. In specialized centers, the proportion of children with HSPN who progress to renal failure or end-stage renal disease varies from 1% to 17%<sup>2-8)</sup>.

It is therefore important to clarify the onset mechanism, clinical manifestations of and ascertain the most appropriate treatment for HSPN. Herein we review the literature on the pathogenesis, clinical manifestations, prognostic factors, and treatment of HSPN.

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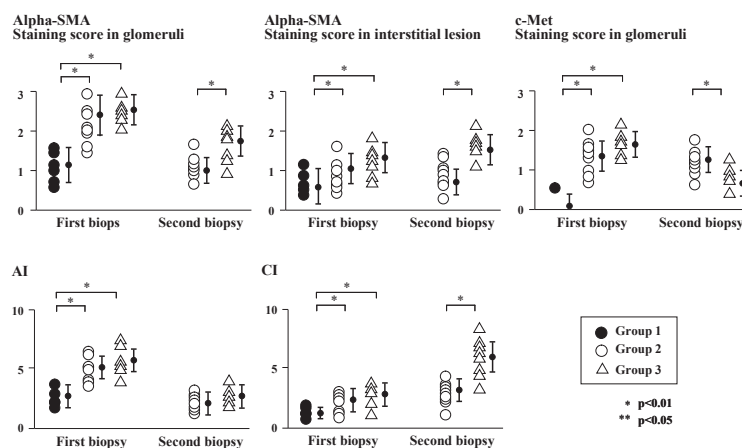


Fig. 1. Renal expression of alpha-smooth muscle actin and c-Met in children with Henoch-Schönlein purpura nephritis.

The mean scores for glomerular and interstitial  $\alpha$ -SMA staining in Groups 2 and 3 were significantly higher than those in Group 1. At the first renal biopsy, none of the patients in Group 1 and all patients in Groups 2 and 3 clearly expressed c-Met in the glomeruli. At the first renal biopsy, AI and CI in Groups 2 ( $p < 0.01$ ) and 3 ( $p < 0.01$ ) were higher than those in Group 1.

#### INCIDENCE OF DISEASE

Gardner-Medwin *et al.* examined the frequency of and ethnic variations in childhood vasculitides in the West Midlands region of the United Kingdom<sup>6</sup>. Their survey was completed using monthly questionnaires sent to consultants and a single questionnaire sent to family doctors, along with a review of case notes with diagnostic codes for vasculitis. The annual incidence of HSP in the study was 22.1 cases per 100,000 children, which was higher than previous estimates of 13.5–18.0 cases per 100,000 children<sup>7,8</sup>. The authors postulated that a higher incidence of HSP may lead to increases in the incidences of renal disease and need for renal medical treatment. Stewart *et al.* evaluated a total of 270 patients with HSP from a total pediatric population of 155,000 over a 13-year period and showed that the incidence of HSPN was 2.7 cases per 100,000 children<sup>7</sup>. The mean incidence of HSPN in Asian children, however, has been reported to be 4.9 cases per 100,000 children per year, and over a 22-year period in Japan, Kawasaki *et al.* reported that the mean number of HSPN cases per 100,000 children per year to be 3.6 $\pm$ 1.0 (Figure 1)<sup>9</sup>.

#### PATHOGENESIS

The pathogenesis of HSP remains unknown; however, HSP is generally believed to be an immune complex-mediated disease characterized by the presence of polymeric IgA1 (pIgA1)-containing immune complexes predominantly in the dermal,

gastrointestinal and glomerular capillaries<sup>10–14</sup>. The pathognomonic granular IgA and C3 deposits in the mesangium are indistinguishable from those seen in IgA nephropathy, and similar immunohistologic findings have been observed in the kidneys of patients with liver cirrhosis, dermatitis herpetiformis, celiac disease, and chronic inflammatory disease of the lung.

Although the pathogenic mechanisms of HSPN have not been fully elucidated, perturbations in the immune system, elevations in the serum levels of IgA1, IgA1-containing circulating immune complexes, circulating IgA-antineutrophil cytoplasmic antibodies (ANCA), and IgA-rheumatoid factors have been documented for patients with HSP<sup>15–19</sup>. Coppo *et al.* also reported elevated serum levels of IgA and IgA-containing immune complexes in patients with HSPN<sup>20</sup>. In addition, it was reported that all HSP patients have IgA1-containing circulating immune complexes of small molecular mass, but only those with nephritis have additional IgA1-IgG-containing circulating immune complexes of large-molecular-mass<sup>21</sup>. Furthermore, using GalNAc-specific lectin from *Helix aspersa*, Lau *et al.* reported that the serum levels of galactose-deficient IgA1 (Gd-IgA1) were higher in children with HSPN than in healthy controls and patients with C1q nephropathy<sup>22</sup>. However, the median levels of serum Gd-IgA1 in children with HSP without nephritis did not significantly differ from those in healthy controls. These data corroborate a potential pathogenic role for Gd-IgA1 in HSPN.

Both increased IgA synthesis and diminished

clearance have been implicated in the pathogenesis of IgA immune complex deposition. Increased polymeric IgA production by the mucosal immune system in response to a mucosally presented antigen, such as bacteria, viruses, or fungi, has been hypothesized as a potential mechanism for the development of HSP<sup>9</sup>. Hyper-reactivity of both B and T cells in response to specific antigenic stimuli *in vitro* has been reported in patients with HSP, resulting in increased polymeric IgA production, including Gd-IgA in mucosal and tonsillar cells<sup>18</sup>. Gd-IgA1, in particular, is currently assumed to have a pivotal role in the pathogenesis of HSPN<sup>22</sup>.

The mechanisms of renal injury by the Gd-IgA1 immunocomplex in HSPN are as follow: 1) The Gd-IgA1 immunocomplex in the mesangial areas activates a complement pathway, such as the alternate or lectin pathways<sup>23</sup>. Deposition of C3 and properdin without C1q or C4 is typical, suggesting alternate pathway activation. Despite the demonstration of complement components in skin and renal biopsies, questions remain regarding the role of the complement system in the pathogenesis of HSP<sup>21-25</sup>. However, Hisano *et al.* found that complement activation through the lectin pathway may contribute to the development of advanced glomerular injuries and prolonged urinary abnormalities in patients with HSPN<sup>25</sup>. 2) The Gd-IgA1 immunocomplex in the mesangial areas activates mesangial cells, which results in the proliferation of cells, such as macrophages and lymphocytes, and the production of inflammatory and profibrogenic cytokines and chemokines, suggesting a pivotal role in mesangial cell proliferation, matrix expansion, and inflammatory cell recruitment<sup>26</sup>. Kawasaki *et al.* reported that the accumulation of macrophages in the glomeruli was a predictor of poor prognosis in HSPN patients<sup>27</sup>.

On the other hand, there have been several reports on endothelial cell dysfunction in HSPN<sup>28,29</sup>. Fujieda *et al.* showed that endothelial cells are damaged in cases of HSPN, and high IgA antiendothelial cell antibody titers and elevated serum thrombomodulin levels may be clinically useful markers of renal involvement in patients with HSPN<sup>28</sup>. Kawasaki *et al.* reported that serum E-selectin concentrations at the time of the first biopsy in patients with HSPN were higher than those at the time of the second biopsy and could be used to evaluate glomerular endothelial dysfunction in HSPN<sup>29</sup>.

## CLINICAL AND LABORATORY FINDINGS

### (1) *Skin*

The characteristic rash is purpuric and is symmetrically distributed over the extensor surfaces of the lower legs and arms and over the sides of the buttocks. It is nearly always present in the area of the lateral malleolus and at times is present only there. It usually begins as a red maculopapular rash that then becomes purpuric and eventually takes on a fawn color as it fades. The patches of purpura may range from tiny to very large. Sometimes the rash does not have a purpuric stage. It does not itch. In children under five years of age, the illness may start with a generalized urticarial rash, which may later become purpuric. Edema of the scalp and face and of the dorsa of the hands and feet is common. Subcutaneous bleeding may occur anywhere and is often seen in the scrotum, eyelids, and conjunctivae<sup>30</sup>.

### (2) *Joints*

Pain, with or without swelling or tenderness, predominantly affects the ankles and knees. Other joints of the hands and feet may also be affected. Periarticular edema of short duration is observed, but there is no residual injury of the joints.

### (3) *Gastrointestinal tract*

Gastrointestinal involvement occurs in approximately two-thirds of cases of HSP, and usually manifests itself as abdominal pain, and symptoms precede the rash in 14% to 36% of patients. Vomiting, diarrhea, periumbilical pain mimicking appendicitis, and bloody stool are the main abdominal symptoms. Major gastrointestinal complications develop in about 5% of patients, with intussusception the most common. Bowel ischemia and infarction, necrosis, intestinal perforation, fistula formation, late ileal stricture, acute appendicitis, massive upper gastrointestinal hemorrhage, pancreatitis, hydrops of the gallbladder, and pseudomembranous colitis are seen infrequently.

### (4) *Renal manifestations*

#### a. **Incidence of renal involvement**

The proportion of patients reported to suffer renal involvement varies between 20% and 80%<sup>1-8</sup>. Part of this variation is attributable to the differences in criteria used to define renal involvement, as well as to the differences in methods used to detect microscopic hematuria. Urinary abnormali-

ties may be transient, and unless repeated checks are performed, may be missed. A study of the surveys referred to above suggests that 20% to 30% of children have macroscopic hematuria, whereas 30% to 70% have albuminuria, or microscopic hematuria, or both, that persists for more than a week. However, increased rates of red cell excretion in urine have been found in all children with HSPN<sup>30</sup>.

#### **b. Renal presentation**

Just as skin, joint, and gut symptoms may occur in any order at any time over a period of several days or weeks, so too may renal manifestations occur at any time. In general, the first urinary abnormality is noted after other symptoms, but hematuria may occasionally be the initial feature. In 30-80% of children with urinary abnormalities, the first abnormality is detected within 4 weeks of onset of the illness. In most of the remainder of cases, urinary abnormalities develop within the next 8 weeks, and a small minority of affected children are found to have urinary abnormalities several months later<sup>30</sup>.

The non-renal manifestations of illness fluctuate over a period of days or weeks before disappearing. Recurrences are common and appear to be particularly common in those in whom severe renal damage has occurred. Meadow *et al.* found that 22 (25%) of 88 children with HSPN suffered a late relapse of the syndrome two months or more after the initial episode. Relapses may occur in association with upper respiratory tract infections<sup>30</sup>.

The most common urinary abnormalities are albuminuria and microscopic hematuria. A smaller number of patients have macroscopic hematuria. Acute nephritic syndrome occurs in the more severe cases and may lead to nephrotic syndrome or renal insufficiency. Both of these may develop independently and insidiously, but they are much more likely to develop in children who experience an acute nephritic stage during the course of the illness.

#### **c. Pathologic Changes**

##### **Immunofluorescence**

In contrast to the frequently focal and segmental nature of the glomerular lesions observed under light microscopy, one of the more striking features noted in immunofluorescence studies is the widespread involvement of glomeruli. These abnormalities are granular deposits of IgA and, to a lesser extent, IgG or IgM<sup>1-8,30</sup>. The later-acting components of the complement sequence, C3 and properdin, are more frequently found than C1q or C4. The deposits are largely mesangial in distribution, with an occasional segmental paramesangial capil-

lary deposit. Fibrin-related antigens are frequently deposited in the mesangial areas.

##### **Light Microscopy**

The basic pattern of glomerular involvement is that of mesangial injury or mesangial proliferative glomerulonephritis with varying degrees of hypercellularity, similar to the lesions seen in IgA nephropathy. Segmental capillary thrombosis, possibly related to the development of necrosis and crescents, is often present<sup>1-8,30</sup>. For classification of the degree of involvement and its correlation with clinical manifestations and prognostic indices, the glomerular changes were graded according to the classification devised by the pathologists of the International Society of Kidney Disease (ISKDC) in children. Patients with grade II and IIIa histological findings tend to have better outcomes, with either return of normal renal function or persistent microscopic hematuria and proteinuria, whereas patients with grade IIIb, IV, and V have persistent proteinuria and hematuria or progress to terminal renal failure<sup>30</sup>. A few patients develop rapidly progressive renal failure accompanied by exuberant crescent formation.

### **DIAGNOSTIC INVESTIGATION**

Diagnosis is made instead on the basis of clinical suspicion, and laboratory tests are mainly directed toward excluding other diagnostic possibilities and assessing the extent of renal involvement. Renal biopsy is particularly useful in distinguishing HSP from other disorders, and in assessing prognosis and indicating the need for treatment for the patients with urinary protein excretion more than 0.5 g/day at 1-2 months after the onset of HSPN.

### **COURSE AND CLINICOPATHOLOGICAL CORRELATIONS**

Although HSP is generally a benign, self-limiting disorder, there may be episodic and recurrent bouts of rash, arthralgia, gastrointestinal symptoms, and hematuria for several months or even years after the initial onset.

In patients with focal and segmental proliferative glomerular lesions, the overall mortality is less than 10% at 5 and 10 years after onset<sup>31-33</sup>. In a large series of patients seen by Meadow *et al.* at 2 years or more after diagnosis, 55% were entirely normal, 22% had residual urinary abnormalities but normal GFR, 10% had both abnormal urine sediment and reduced GFR, and 8% had a severe reduction in GFR, were receiving dialysis, or had died of

renal failure<sup>33</sup>).

Kawasaki *et al.* investigated the cases of HSPN for whom long-term follow-up was available and enrolled 114 patients who had been diagnosed with HSPN between 1974 and 1997<sup>27</sup>. These patients were divided into 2 groups based upon features at the last follow-up. One group, designated “favorable”, consisted of 69 patients with normal urine and 25 patients with minor urinary abnormalities, and the second group, designated “unfavorable”, consisted of 15 patients with active renal disease and 5 patients with renal failure. The clinical features, laboratory data and pathological findings were investigated for the 2 groups (Tables 1 and 2). Nephrotic syndrome, decreased factor XIII activity, hypertension and renal failure at onset were more frequent in the “unfavorable” than in the “favorable” group. The rate of glomeruli with crescents, macrophage infiltrations, tubulointerstitial changes and acute exacerbation in the “unfavorable” group were

higher than those in the “favorable” group. There were 5 cases with renal insufficiency and the renal survival rate for 15 years or over was 95.6%. These results suggest that the abovementioned risk factors play an important role in the prognosis of patients with active renal disease and renal failure.

As to the other prognostic factors, Kawasaki *et al.* reported that the expression of renal alpha-SMA was a predictor of poor prognosis in HSPN patients<sup>34</sup>. Alpha-smooth muscle actin (alpha-SMA) is the predominant actin isoform within vascular smooth-muscle cells and plays an important role in fibrogenesis. On the other hand, c-Met is the receptor for hepatocyte growth factor (HGF), which plays a role in protection from injury and has anti-fibrogenetic effects. Kawasaki *et al.* evaluated the renal expression of alpha-SMA and c-Met in HSPN patients (Figure 1). Patients were divided into three groups. Group 1 consisted of eight patients (male : female 4 : 4) classified as International Study of

Table 1. Comparison of clinical manifestations, laboratory data and pathological findings at onset in both groups.

		“Favorable” (n=94)	“Unfavorable” (n=20)	
Clinical manifestation				
Purpura	114 (100%)	94 (100%)	20 (100%)	NS
Abdominal pain	29 ( 25%)	23 ( 24%)	6 ( 30%)	NS
Arthralgia	11 ( 10%)	8 ( 9%)	3 ( 15%)	NS
Quincke edema	9 ( 8%)	7 ( 7%)	2 ( 10%)	NS
AGN	9 ( 8%)	3 ( 3%)	6 ( 40%)	<i>p</i> <0.01
NS	17 ( 15%)	9 ( 10%)	8 ( 60%)	<i>p</i> <0.01
RPGN	4 ( 4%)	0 ( 0%)	4 ( 25%)	<i>p</i> <0.05
School urinary screening	4 ( 4%)	4 ( 4%)	0 ( 0%)	NS
Intussusception	1 ( 1%)	1 ( 1%)	0 ( 0%)	NS
Laboratory data				
Proteinuria (mg/m <sup>2</sup> /h)		58 (71)	146 (104)	<i>p</i> <0.05
Hematuria		92 (98%)	20 (100%)	NS
Serum albumin (g/dl)		36±10	26±8	<i>p</i> <0.05
Serum creatinine (mg/l)		4.9±2.8	8.8±5.0	<i>p</i> <0.05
24-h creatinine clearance (ml/min/1.73 m <sup>2</sup> )		96.9 (29.9)	70.8 (20.4)	<i>p</i> <0.05
Mean blood pressure (mmHg)		80±10	93±14	<i>p</i> <0.05
ISKDC classification				
Type II		31 ( 33%)	0 ( 0%)	<i>p</i> <0.05
Type IIIa		24 ( 26%)	1 ( 5%)	NS
Type IIIb		21 ( 22%)	6 ( 30%)	NS
Type IVb		16 ( 17%)	7 ( 35%)	NS
Type Vb		2 ( 2%)	3 ( 15%)	<i>p</i> <0.05
Type VI		0 ( 0%)	3 ( 15%)	<i>p</i> <0.01

NS=not significant

Table 2. Comparison of immunofluorescence and light microscopic findings in both groups at the first and second biopsies.

Pathological finding		First biopsy			Second biopsy		
		“Favorable”	“Unfavorable”	<i>p</i>	“Favorable”	“Unfavorable”	<i>p</i>
IF findings	IgG	0.3 (0.3)	0.6 (0.5)	NS	0.6 (0.2)	1.8 (0.5)	<i>p</i> <0.01
	IgA	2.5 (0.6)	2.7 (0.7)	NS	2.3 (0.5)	2.1 (0.8)	NS
	IgM	0.3 (0.4)	0.2 (0.3)	NS	0.5 (0.2)	1.2 (0.4)	<i>p</i> <0.05
	C1q	0.1 (0.2)	0.1 (0.2)	NS	0.0 (0.0)	0.1 (0.2)	NS
	C3	1.2 (0.8)	1.4 (0.9)	NS	1.5 (0.7)	1.1 (1.2)	NS
	C4	0.2 (0.3)	0.0 (0.0)	NS	0.0 (0.0)	0.0 (0.0)	NS
	Fib	2.5 (0.6)	1.8 (1.1)	NS	1.8 (1.7)	2.2 (0.8)	NS
Acute findings							
	Mesangial proliferation	2.0±0.5	1.8±1.1	NS	1.2±0.8	1.3±1.3	NS
	Cellular crescent	1.0±1.0	2.1±1.7	<i>p</i> <0.01	0.4±0.4	0.5±0.9	NS
	Macrophage infiltration in glomeruli	3.8±1.3	11.4±6.1	<i>p</i> <0.05	0.6±0.5	2.2±0.6	<i>p</i> <0.05
	Interstitial mononuclear inflammation	0.9±0.6	2.2±0.5	<i>p</i> <0.01	0.9±0.5	1.8±0.8	NS
	Acute index	7.7±3.4	17.5±9.4	<i>p</i> <0.01	3.1±2.2	5.8±3.6	<i>p</i> <0.01
Chronic findings							
	Glomerular sclerosis	0.6±0.4	1.4±0.9	<i>p</i> <0.05	0.6±0.4	1.4±0.9	<i>p</i> =0.07
	Fibrous crescent	0.3±0.5	0.4±0.9	NS	0.7±0.7	1.8±1.1	<i>p</i> <0.05
	Tubular atrophy	0.5±0.7	1.5±0.5	<i>p</i> <0.05	0.7±0.4	2.1±0.9	<i>p</i> <0.05
	Interstitial fibrosis	0.3±0.4	1.2±0.8	<i>p</i> <0.05	0.7±0.6	1.9±0.7	<i>p</i> <0.05
	Chronicity index	1.7±2.0	4.5±3.1	<i>p</i> <0.01	2.7±2.1	7.2±3.6	<i>p</i> <0.01

NS=not significant

Kidney Disease in Children (ISKDC) grade II or lower; Group 2 consisted of 20 patients (male : female 11 : 9) with ISKDC grade III or greater and a good prognosis, and Group 3 consisted of seven patients (male : female 3 : 4) with ISKDC grade III or greater and poor prognosis. Renal biopsy findings, including c-Met and alpha-SMA staining, were investigated for each group. At first biopsy, the mean scores for renal alpha-SMA and glomerular c-Met in Groups 2 and 3 were higher than those in Group 1, while there were no differences in mean scores for renal alpha-SMA and glomerular c-Met between Groups 2 and 3. At second biopsy, the mean scores for renal alpha-SMA staining in Group 3 were higher than those in Group 2, and mean score for glomerular c-Met staining in Group 3 was lower than that in Group 2. In Groups 2 and 3, the mean scores for glomerular and interstitial alpha-SMA staining at first biopsy were correlated with the chronicity index (CI) at second biopsy, but the mean score for glomerular c-Met staining at first biopsy was not correlated with either the activity index (AI) or CI at the first or second biopsies in any group. Our findings suggest that the expression of renal alpha-SMA may be associated with the pro-

gression of renal injury in HSPN.

In addition, Kawasaki *et al.* evaluated whether serum MRP8/14 complex, which is a marker of monocyte and neutrophil activation, is associated with the clinical manifestations and pathological findings of HSPN<sup>35</sup>. Patients were divided into two groups based on serum MRP8/14 complex levels at renal biopsy. Group 1 consisted of 18 HSPN patients with lower than median (670 ng/ml) MRP8/14 complex levels, and Group 2 of 12 HSPN patients with greater than median levels. Clinical manifestations, laboratory findings and serum E-selectin levels, as a marker of vascular endothelial cell dysfunction, as well as histological and immunohistochemical findings were investigated for both groups. Kawasaki *et al.* also measured MRP8/14 complex levels in disease control and healthy control children. Urinary protein excretions, serum MRP8/14 complex levels, and serum E-selectin levels were all higher in Group 2 than in Group 1 patients. Serum MRP8/14 complex levels were higher in HSPN patients than in the controls. Serum MRP8/14 complex levels were strongly associated with serum E-selectin levels (Figure 2). Pathological findings revealed that the

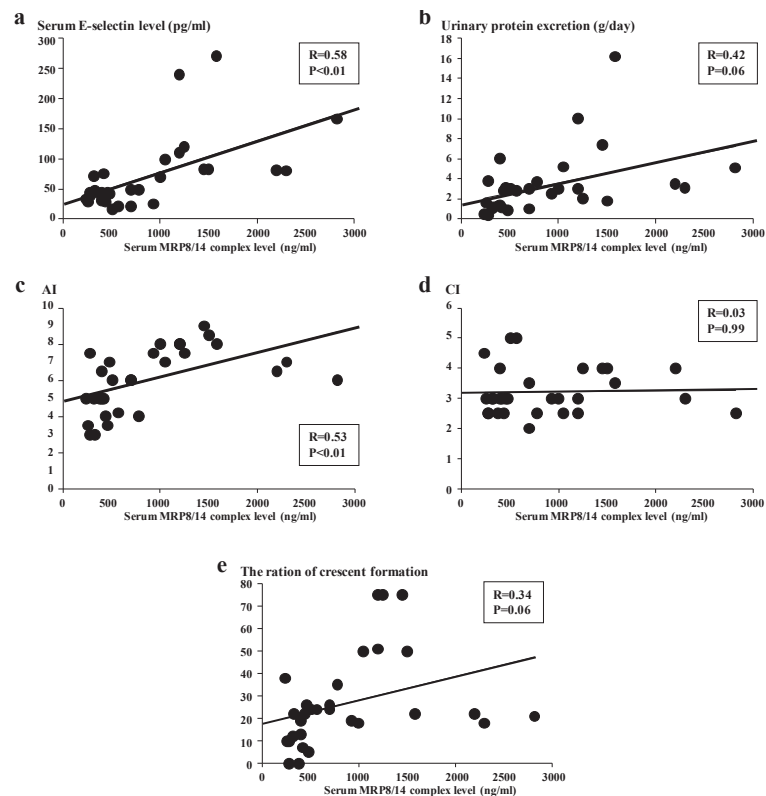


Fig. 2. Relationships among serum E-selectin level, urinary protein excretion, AI, CI, the degree of crescent formation, and serum MRP8/14 complex level.

- Serum E-selectin level was associated with serum MRP8/14 complex level ( $R=0.58$ ,  $p<0.01$ ).
- Urinary protein excretion tended to be associated with serum MRP8/14 complex level ( $R=0.42$ ,  $p=0.06$ ).
- AI was associated with serum MRP8/14 complex level ( $R=0.53$ ,  $p<0.01$ ).
- CI was not associated with serum MRP8/14 complex level ( $R=0.03$ ,  $p=0.99$ ).
- The degree of crescent formation tended to be weakly associated with serum MRP8/14 complex level ( $R=0.34$ ,  $p=0.06$ ), AI activity index, CI chronicity index.

proportions of patients with ISKDC grades III, IV and V in Group 2 were higher than in Group 1. Our findings suggest that serum MRP8/14 complex levels might be associated with the severity of renal injury and endothelial cell dysfunction in HSPN patients.

In a long-term follow-up of 78 patients with an average observation period of 23 years after the onset of HSPN in childhood, Goldstein *et al.* noted that 44% of patients presenting with nephrotic syndrome or acute nephritis had persisting hypertension or a progressive decline in GFR, whereas 82% of those who presenting with hematuria alone were normal. Sixteen of 44 full-term pregnancies were also complicated by proteinuria and/or hypertension, even in the absence of active renal disease<sup>32</sup>. Subsequent deterioration in clinical status was observed in approximately 20 to 25% of patients, even after initial and apparently full recovery, indicating the need for the long-term follow-up of patients with HSP<sup>32</sup>.

## TREATMENT OF HSPN

The extrarenal manifestations of HSPN are managed by appropriate symptomatic measures. Severe skin lesions may require oral corticosteroids<sup>13,37-39</sup>, which may also improve abdominal pain and protein-losing enteropathy<sup>37</sup>. Severe gastrointestinal complications may occasionally require surgical intervention<sup>30</sup>.

As for the treatment of HSPN, there have been many reports dealing with the use of corticosteroids and multiple combined agents, including immunosuppressive drugs.

### (1) The efficacy of steroids

A majority of patients with HSPN have either no clinical renal involvement or demonstrate microhematuria, mild proteinuria, and normal renal function. These patients do not require steroid therapy, and the disease is usually managed symptomatically. Niaudet *et al.*<sup>39</sup> reported that MPT is effec-



tive for patients at the risk of progression of nephropathy. Another study appeared to confirm that the early administration of prednisone is useful in preventing the development of HSPN<sup>40</sup>. In an uncontrolled study, Kawasaki *et al.* performed a long-term observation of the clinical manifestations and prognosis of 56 patients undergoing methylprednisolone and urokinase pulse therapy (MUPT). The mean urinary protein excretion after 6 months of treatment was found to have decreased significantly compared with the "pre-MUPT" level. Hypercoagulant status "after the completion of urokinase pulse therapy" was also improved compared with the "pre-MUPT" status. First renal biopsies were performed in all patients, and second biopsies were performed in 27 patients. The activity index decreased significantly from 4.1  $\pm$  1.9 at the first biopsy to 2.5  $\pm$  1.7 at the second biopsy, whereas there were no differences in chronicity index between the first and second biopsies. No patients showed any renal insufficiency and the renal survival rate was 100% for the decade. These results suggested that MUPT is effective for those patients at risk of progression of nephropathy, particularly if started early in the course of the disease before the crescents become fibrous. Urokinase is a plasminogen activator derived from fresh human urine that first attracted attention as a therapeutic agent for thrombotic diseases such as cardiovascular diseases or cerebral thrombosis. The rationale for such treatment was as follows: 1) stronger defibrinating activity was observed with urokinase administration than with anti-coagulant drug administration, 2) specific accumulations of urokinase were seen in the kidney and liver despite a very short turn-over rate, and 3) adverse effects were very rare, even when urokinase was administered for a long period<sup>41</sup>.

## (2) *The efficacy of multiple-drug therapy*

A prospective study of 12 patients with HSP who presented with rapidly progressive glomerulonephritis suggested benefits could be derived from intensive multiple-drug therapy<sup>42</sup>. Clinical improvement associated with combined corticosteroid and azathioprine therapy was also suggested by another study of 21 children with severe HSPN<sup>43</sup>. Iijima *et al.* showed that multiple combined therapy including prednisolone, cyclophosphamide, heparin/warfarin, and dipyridamole was effective in the treatment of histologically severe HSN<sup>44</sup>. In addition, Flynn *et al.*<sup>45</sup> reported that treating children with HSPN with high-dose corticosteroids plus oral cyclophosphamide is safe and, as in nephrotic syn-

drome, appears to significantly reduce proteinuria. This study, however, was not a controlled study. Therefore, Kawasaki *et al.* evaluated the efficacy of methylprednisolone and urokinase pulse therapy combined with cyclophosphamide for patients with HSPN. They studied 37 patients who had been diagnosed with HSPN of at least ISKDC grade IVb. Of them, 20 (Group A) were treated with methylprednisolone and urokinase pulse therapy, and 17 (Group B) were treated with methylprednisolone and urokinase pulse therapy combined with cyclophosphamide. Methylprednisolone and urokinase pulse therapy combined with cyclophosphamide, but not methylprednisolone and urokinase pulse therapy alone, was found to significantly reduce urinary protein excretion (Figure 3) and prevent any increase in crescentic or sclerosed glomeruli in HSPN patients with at least ISKDC grade IV HSPN. At the most recent follow-up, none of the patients treated with methylprednisolone and urokinase pulse therapy combined with cyclophosphamide were observed to have persistent nephropathy or renal insufficiency<sup>46</sup>. Shin *et al.* suggest that CyA therapy is also effective in reducing proteinuria, which is a known risk factor for the development of renal insufficiency in HSPN and may lead to a regression in renal pathology in patients with nephrotic-range proteinuria<sup>47</sup>.

However, some problems, such as anemia, leukopenia, alopecia, hemorrhagic cystitis, carcinogenesis, and hypogonadism, remain with the use of the above immunosuppressive drugs. Thus, Kawasaki *et al.* evaluated whether methylprednisolone and urokinase pulse therapy combined with mizoribine, which has only mild side effects and is comparatively safe, (MUPM) was effective in children with severe HSPN. They studied 12 patients who had been diagnosed with HSPN of at least ISKDC grade III. All patients were treated with MUPM and clinical features, pathological findings, and prognosis were investigated prospectively. Ten patients (responders; nine with ISKDC grade IIIb and one with grade IVb) were treated with MUPM, whereas MUPM was discontinued due to a lack of response in two patients (non-responders; both with grade IVb). Among the responders, urinary protein excretion had decreased significantly from 99.7 $\pm$ 37.8 to 25.9 $\pm$ 33.4 mg/m<sup>2</sup> per hour after 3 months of therapy. The acute index and tubulointerstitial scores decreased significantly from 5.8 $\pm$ 1.5 and 3.8 $\pm$ 0.6 at the first biopsy to 2.3 $\pm$ 1.3 and 1.0 $\pm$ 0.8 at the second biopsy, respectively. At the most recent follow-up, eight of the responders had normal urine,

and two had minor urinary abnormalities. The non-responders demonstrated continued high levels of urinary protein excretion after 3 months of therapy, and MUPM was discontinued. These results suggest that MUPM is effective in ameliorating proteinuria and the histological severity of HSPN in patients with <50% crescents, but is not so effective for HSPN in patients with >50% crescents<sup>48</sup>.

On the other hand, Ninchoji *et al.* retrospectively reported that patients with moderately severe HSPN (histological grade I-III and serum albumin [Alb] >2.5 g/dl), who were treated with angiotensin-converting enzyme inhibitors and/or angiotensin receptor blockers, showed resolution of proteinuria without renal dysfunction during the observation period (3.76±0.37 years). Thus, aggressive therapies, particularly combination therapies, are unnecessary for moderate-severe HSPN<sup>49</sup>.

### (3) Plasmapheresis

There have been a number of reports on plasmapheresis (PP) for HSPN in childhood<sup>50,51</sup>. Hattori *et al.* retrospectively evaluated the clinical courses of nine children with a rapidly progressive type of HSPN who were treated with plasmapheresis (PP) as the sole therapy. All patients had nephrotic-range proteinuria (4.9+/-2.5 g/m<sup>2</sup>/d, mean+/-SD) and decreased glomerular filtration rate (GFR) (46.5+/-9.5 mL/min/1.73 m<sup>2</sup>) at the time of the initiation of PP. Biopsy specimens taken before PP showed large crescents involving more than 50% of the glomerular circumference in 56.8+/-6.9% of the glomeruli examined. The mean interval between disease onset and initiation of PP was 39.1+/-22.1 days. The PP regimen consisted of thrice-weekly treatment for 2 weeks, then weekly treatment for 6 weeks. All patients responded promptly to PP with improvement in renal function, reduction of proteinuria, and subsidence of purpuric rash and abdominal pain. Six of nine patients showed further improvements without any other treatment; four recovered completely, and two had only microscopic hematuria at the latest observation (follow-up period, 9.6+/-4.3 years). The remaining three patients showed a rebound increase in proteinuria after the completion of PP; two of whom progressed to end-stage renal failure at 14.1 years and 1.8 years, respectively, after disease onset. These results suggest that PP as the sole therapy is effective in improving the prognosis of patients with rapidly progressive HSP nephritis, particularly if instituted early in the course of the disease<sup>50</sup>.

On the other hand, Kawasaki *et al.* reviewed the cases of six Japanese children with rapidly progressive HSPN who received multiple drug therapy combined with PP. After five courses of PP, multiple drug therapy, including methylprednisolone and urokinase pulse therapy, oral prednisolone, cyclophosphamide, dipyridamole, and warfarin, was given. At presentation, urine protein excretion and histological indices of the mean activity and chronicity were 245+/-101 mg/m<sup>2</sup> 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 was also decreased significantly at the second renal biopsy performed at a mean interval of 4.3 months after the first biopsy (2.8+/-1.4,  $P<0.05$ ), whereas there was no change in the chronicity index. At the most recent observation, all patients showed clinical improvement. Two patients had normal urine, three had proteinuria of <20 mg/m<sup>2</sup> per hour, one had proteinuria of >20 mg/m<sup>2</sup> per hour, and none showed any renal insufficiency. Although this case series was examined without controls, this treatment protocol may be of benefit to children with rapidly progressive HSPN<sup>51</sup>.

The benefits of the abovementioned treatments for treating HSPN deserve to be assessed further in larger randomized controlled trials.

### (4) Other types of treatment

The use of intravenous immunoglobulin (IVIg) for the treatment of HSP is anecdotal and has been advocated as effective for abdominal pain and other gastrointestinal symptoms<sup>52</sup>.

Some studies have reported that tonsillectomy was effective for patients with severe HSPN<sup>53-55</sup>. Kawasaki *et al.* reported an 11-year-old boy with HSPN accompanied by recurrent purpura and persistent nephropathy despite conventional therapy such as prednisolone, methylprednisolone pulse therapy and mizoribine. The patient was treated with tonsillectomy plus methylprednisolone pulse therapy. This treatment decreased proteinuria, induced the disappearance of microscopic hematuria, and improved renal pathological findings. This case suggests that tonsillectomy plus methylprednisolone pulse is an effective and useful therapy for some children with recurrent purpura and persistent nephropathy<sup>54</sup>. Furthermore, Ohara *et al.* reported a 13-year-old girl with HSPN of ISKDC grade VI and persistent nephrotic syndrome despite receiving conventional therapy such as prednisolone, methylprednisolone and urokinase pulse therapy and plas-

Table 3. Treatment of HSPN in our hospital.

Severity		Treatment
ISKDC	I or II	Antiplatelet agents
	III	Steroid+antiplateletagents+anticoagulant Or Methylprednisolone+urokinase pulse+steroid+antiplatelet agents+anticoagulant (MUT) and/or mizoribine
	IV	MUT with cyclophosphamideor mizoribine
	V	MUT with cyclophosphamide
	VI	MUT with cyclophosphamide
Patients with rapidly progressive HSPN		MUCT with plasmapheresis
Patients with ISKDC III a presenting as nephroticsyndrome		MUT

mapheresis (PP). The patient was treated with tonsillectomy, which subsequently decreased proteinuria, induced the disappearance of microscopic hematuria, and improved renal pathological findings. A regimen of methylprednisolone and urokinase pulse therapy plus PP with tonsillectomy may be an effective and useful therapy for some children with severe HSPN children of ISKDC grade VI and persistent nephrotic syndrome<sup>55</sup>.

#### (5) Transplantation

HSPN may recur after transplantation, and rates of recurrence are increased in recipients of living-related transplantations<sup>56,57</sup>. Meulders *et al.* reported the actuarial risks for renal recurrence and graft loss due to recurrence to be 35 and 11%, respectively, at 5 years after transplantation<sup>56</sup>. Recurrence appeared to be associated with shorter duration of the original episode of disease, occurrence despite delays of more than 1 year between the disappearance of purpura and transplantation, and was not prevented by a triple immunosuppressive regimen that included CyA.

Finally, our recommendations for the treatment of HSPN in our hospital are shown in Table 3. We try to perform renal biopsy at 1-2 months after the onset of HSPN for patients with a urinary protein excretion of more than 0.5 g/day, and provide aggressive therapy according to the severity of pathological lesions. We believe these treatments are effective in improving the prognosis for HSPN.

#### CONCLUSION

We have reviewed the pathogenesis, clinical manifestations, prognostic factors of and treatment for HSPN, including multiple drug combination therapies. Further detailed investigation of HSPN pathogenesis and treatment is necessary to identify

the most appropriate treatment.

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