Correlation Between Clinicaland Pathological Characteristics of Henoch-Schönlein Purpura Nephritis in Adults

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Introduction. Henoch-Schönlein purpura nephritis (HSPN) mainly affects children and is less common in adults, but its associated pathological changes are severe in adults, in whom it results in a poor prognosis. This study aimed to analyze the clinical and pathological characteristics of HSPN in adults and to identify the correlations among them.

Materials and Methods. Clinical and pathological data from139 patients older than 18 years of age who had been diagnosed with HSPN and had received renal biopsy at our center from January 2012 to November 2014 were collected and were grouped according to the different conditions and analyzed retrospectively.

Results. The 139 HSPN patients included 74 men and 65 women, with an average age of 39.17 ± 15.87 years. The pathological grade was IIIa in most of the patients, and moderate proteinuria was the most common clinical type. Kidney failure and 24-hour total urinary protein, serum uric acid, cystatin C, and β2-microglobulin levels were positively correlated with the pathological grade and activity ($P < .05$). Age, kidney failure, and uric acid were positively correlated with the pathological chronicity ($P < .05$).

Conclusions. The clinical characteristics of the adult HSPN patients were correlated with the severity of the renal pathology. It is feasible to predict renal pathological changes according to the clinical manifestations of adult HSPN patients.

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INTRODUCTION

Henoch-Schönlein purpura (HSP) is a systemic vasculitis mainly affecting the skin, joints, gastrointestinal tract, and kidneys. The resulting renal impairment is called Henoch-Schönlein purpura nephritis (HSPN), which has an incidence rate of 20% to 80%.[1,2] Henoch-Schönlein purpura nephritis is the most serious complication of HSP and affects the prognosis.[3,4] It occurs mainly in children and is less common in adults,[1] but represents a more severe clinical syndrome, with a higher frequency of renal involvement.[5]

In the past, the clinical manifestations of HSPN have been considered mild and self-limiting, especially in pediatric patients. However, in recent years, the incidence of end-stage renal disease in HSPN patients has shown an increasing trend. In children, approximately 5% to 15% of HSPN cases progress to chronic kidney failure,[6] while the incidence is approximately 11% to 30% in adults.[7,8] The severity of renal impairment determines the disease prognosis.[9] The comprehensive assessment of renal impairment in these patients is beneficial for the development of an effective therapy.

Because the incidence of HSPN in children is higher than that in adults, recent clinical studies

have mainly focused on the clinical diagnosis and treatment of pediatric HSPN and the comparison of its characteristics between adults and children.[10-12] Independent analyses of the clinical and pathological characteristics of adult HSPN and the correlations among these characteristics are rare. However, adult HSP had a higher rate of renal involvement and worse prognosis.[7-9,12] Thus, independent analysis of the characteristics of adult HSPN is extremely important. The purpose of this study was to retrospectively analyze the clinical and pathological characteristics of adult HSPN cases treated at our hospital and the correlations among these characteristics.

MATERIALS AND METHODS

This study was approved by the ethics committee of the First Affiliated Hospital of Zhengzhou University in China. The study included a total of 139 patients older than18 years of age who had been diagnosed with HSPN and had received renal biopsy at our center from January 2012 to November 2014. All patients were diagnosed according to the following criteria[13]: a history of typical skin purpura, varying degrees of renal impairment (such as proteinuria, hematuria, and kidney failure), and skin purpura that was not associated with thrombocytopenia or coagulation disorder, as well as 1 or more of the following symptoms: diffuse abdominal pain, arthritis or arthralgia, and immune complex deposition, mainly consisting of immunoglobulin A (IgA), based on the tissue biopsy findings.

The patients' demographics, symptoms, laboratory data, and pathological changes (eg, grade, activity index [AI], and chronicindex [CI]) were abstracted from the medical records. An estimated glomerular filtration rate less than 60 mL/min was defined as kidney failure, and the Modification of Diet in Renal Disease equation was used to calculate this value. An average blood pressure reading of greater than 140/90 mm Hg on 3 consecutive measurements was defined as hypertension. Hyperuricemia was defined by a serum uric acid level of 416 µmol/L (7.0 mg/dL) and greater in males or 357 µmol/L (6 mg/dL) and greater in females.[14] According to the erythrocyte count in the urine under a high-power field (HPF), microscopic hematuria was defined as follows: 1+ (5 to 19 per HPF), 2+ (20 to 30 per HPF), 3+ (> 30 per HPF), and 4+ (full field per HPF). The patients were divided into the following 4 groups based on their clinical types[12,13]: group A, the simple hematuria group (urine erythrocyte > 5 per HPF and proteinuria < 150 mg/d); group B, the microalbuminuria group (150 mg/d ≤ proteinuria < 1 g/d, with or without hematuria); group C, the moderate proteinuria group (1 g/d ≤ proteinuria < 3.5 g/d, with or without hematuria); and group D, the massive proteinuria group (proteinuria ≥ 3.5 g/d, with or without hematuria).

All of the patients agreed to undergo renal biopsy without contraindications. Immunofluorescence, hematoxylin-eosin, periodic acid-Schiff, Masson, and periodic acid-Schiff plus Masson staining were performed on the pathological tissues. The pathological results were assessed by the pathologist of the hospital. The pathological grades were classified as levels I to VI in accordance with the International Study of Kidney Diseases in Children (ISKDC) classifications,[15] and pathological activity and chronicity were evaluated using the AI and CI scores according to the scoring system developed by Foster and colleagues.[16]

The SPSS software (Statistical Package for the Social Sciences, version 17.0, SPSS Inc, Chicago, IL, USA) was used for statistical analysis. The clinical and laboratory data of countsare presented as the number of cases (percentage), whereas the data of continuous measurements are presented as the mean ± standard deviation. Comparisons of the counts between the groups were conducted using the chi-square test, while those of the measurements were performed using the *t* test. The correlations between the clinical manifestations and pathological changes were analyzed using the Spearman correlation coefficient.

RESULTS

The 139 adult patients with purpura nephritis included 74 men and 65 women, with a male-female ratio of 1.14:1. The onset ages were 18 to 78 years, with an average age of 39.17 ± 15.87 years, and the mean disease duration was 14.84 ± 42.61 months. Twenty-four patients (17.3%) had some type of stimulus, such as infection, drug use, or food allergy. Skin purpura was observed in all of the patients, most commonly in both lower extremities. The clinical manifestations included

arthralgia in 37 patients (26.6%), abdominal pain in 37 (26.6%), melena in 21 (15.1%), and intestinal obstruction in 6 (4.3%). Kidney involvement was diverse and included microscopic hematuria in 109 patients (78.4%), kidney failure in 17 (12.2%), and hypertension in 40 (28.8%). The mean serum uric acid value was 299.92 ± 103.60 μmol/L, and 20 patients (14.4%) were hyperuricemia. The mean serum cystatin C value was 1.14 ± 0.61 mg/L, and the mean serum β2-microglobulin value was 2.52 ± 1.95 mg/L.

Pathological immunofluorescence analysis of the kidneys of all patients showed varying degrees of IgA deposition. Grade IIIa HSPN was the most common pathologicalgrade, observed in a total of 86 patients (61.9%), followed by grade II, detected in 29 patients (20.9%). With regard to the clinical type, moderate proteinuria was the most common, observed in a total of 55 patients (39.6%), followed by microalbuminuria, detected in 46 patients (33.1%). The result of correlation analysis of the clinical types and pathological grades of HSPN patients was not significant (r = 0.137, *P* = .11; Table 1).

With regard to the renal pathology of the patients, the average AI score was 5.71 ± 2.47, and the average CI score was 1.10 ± 1.53. Correlation analyses of the

Table 1. Relationships Between Clinical Types and Pathological Grades*

	Pathological Grade						
Study Groups	**II**	**IIIa**	**IIIb**	**IV**	**V**	**r**	***P***
Group A	0	1 (0.7)	0	0	0		
Group B	14 (10.0)	24 (17.3)	7 (5.0)	1 (0.7)	0		
Group C	10 (7.2)	38 (27.3)	5 (3.6)	2 (1.4)	0		
Group D	5 (3.6)	24 (17.3)	5 (3.6)	2 (1.4)	1 (0.7)	0.137	.11

*Group A had simple hematuria; group B, microalbuminuria; group C, moderateproteinuria; and group D, massive proteinuria.

Table 2. Correlation Analysis of Clinical and Pathological Manifestations

Parameter	**Pathological Grade**		**Activity Index**		**Chronic Index**	
	r	***P***	**r**	***P***	**r**	***P***
Sex	0.053	.54	0.138	.11	0.002	.98
Age	-0.098	.25	-0.021	.80	0.238	.01
Disease duration in months	0.170	.046	0.079	.36	0.106	.22
Kidney failure	0.222	.03	0.325	.00	0.364	< .001
Gross hematuria	0.093	.28	0.117	.17	0.028	.75
Edema	0.176	.04	0.171	.04	0.033	.70
Stomach ache	-0.014	.87	0.036	.67	-0.175	.04
Melena	0.063	.46	0.138	.10	0.116	.18
Intestinal obstruction	-0.033	.70	-0.061	.48	0.014	.87
Arthralgia	-0.063	.46	0.001	.99	0.025	.77
Hypertension	-0.087	.31	-0.011	.89	0.128	.13
Microscopic hematuria	0.191	.04	0.093	.32	-0.059	.54
24-hurinaryprotein	0.231	.01	0.274	.002	0.055	.52
Serum albumin	-0.129	.13	-0.134	.12	0.060	.49
Uric acid	0.186	.03	0.204	.02	0.860	.01
Cystatin	0.297	.002	0.293	.00	0.091	.37
β2-microglobulin	0.292	.003	0.25	.01	0.101	.31
Total cholesterol	-0.022	.80	-0.024	.78	0.056	.51
Triglycerides	0.027	.75	0.062	.47	-0.029	.73
High-density lipoprotein	-0.026	.77	-0.146	.09	-0.014	.87
Low-density lipoprotein	-0.027	.76	0.004	.97	0.072	.41
Leukocytes	-0.029	.74	-0.087	.31	-0.058	.50
Hemoglobin	-0.181	.03	-0.144	.09	-0.052	.55
Platelets	0.098	.25	0.028	.75	-0.022	.80
Erythrocyte sedimentation rate	-0.006	.95	0.061	.51	0.021	.82
C-reactive protein	0.015	.88	0.149	.11	0.141	.13
Complement C3	0.061	.51	0.087	.35	-0.012	.90

clinical manifestations, pathological grades, and AI/CI scores revealed that the disease duration in months, the presence of kidney failure, microscopic hematuria, 24-hour urinary protein, serum uric acid, cystatin C, and β2-microglobulin levels were positively correlated with the pathological grade, whereas the hemoglobin concentration exhibited a negative correlation ($P < .05$). Kidney failure and the 24-hour urinary protein, uric acid, cystatin C, and β2-microglobulin levels were positively correlated with the AI score ($P < .05$). Age, kidney failure, and serum uric acid level were positively correlated with the CI score, whereas abdominal pain exhibited a negative correlation ($P < .05$; Table 2).

DISCUSSION

Currently, the pathological progression of HSPN is generally considered to be similar to that of IgA nephropathy,[17] and its treatment is usually the same as that of IgA nephropathy. However, a recent study[18] has shown that compared to IgA nephropathy, the pathological progression of HSPN results in a greater increase in the proliferation of endothelial cells and IgA deposition in the capillary loop, suggesting that this condition results in more obvious vasculitis damage; thus, it is important to analyze the pathological performance of HSPN independently. Renal involvement is a decisive factor in HSP prognosis. The incidence of renal involvement in adult HSP is high, and the risk of progression to kidney failure is even greater for older-aged patients.[19,20] Additionally, our preliminary results indicated that the pathological changes in adults were severe.[21] In this study, renal pathological grade IIIa was the most common, accounting for 61.9% of the cases, and 23 HSPN patients showed pathological grade IIIb or higher, accounting for 16.5% of the cases, demonstrating more severe pathological changes compared to those previously reported in the literature.[22]

In this study, the renal pathological damage and extrarenal symptoms (arthralgia and gastrointestinal involvement) have no correlation, but proteinuria and kidney failure are closely related to the severity of renal damage. Ye and coworkers[23] reported that in pediatric HSPN patients, 24-hour urinary protein concentration might be predictive of the pathological grade; grades IIb, IIIa, and IIIb were the most common in patients with a high 24-hour urinary protein concentration. Coppoet and colleagues[24] showed that the clinical symptoms in adults had more predictive power than those in children and that renal insufficiency, proteinuria (> 1.5 g/24 hours), and hypertension were negative prognostic factors. The results of this study revealed that the 24-hour urinary protein level and kidney failure displayed the strongest correlation with the pathological grade and AI score in adult HSPN. The AI reflects the severity of pathological changes, including mesangial proliferation, crescent formation, and necrosis, suggesting that patients with massive proteinuria and kidney failure likely have severe pathological changes, indicating that active therapy should be performed. In this study, the clinical types and pathological grades were not correlated, but the 24-hour urinary protein and microscopic hematuria levels were positively correlated with the pathological grade. One reason for these results may be that some patients had mild proteinuria but severe hematuria; thus, the severity of both proteinuria and hematuria should be evaluated in adult HSPN patients.

The poor prognosis of adult HSPN patients may be related to the high degree of renal chronicity. Previous studies have shown that the high degree of renal interstitial fibrosis, glomerular sclerosis, and fibrinoid necrosis in adult HSPN patients are indicative of a poor prognosis.[22] In this study, we used a detailed method to calculate the CI score that included these indicators, and the patients with a high CI score might have a poor prognosis. We found that the patients with old age, kidney failure, and hyperuricemia had a high CI score and thus might have a poor prognosis. In previous studies, the pathological grading of adult HSPN has been mainly based on the ISKDC standards, and the AI and CI scores have rarely been used to assess the degree of renal impairment. The ISKDC standards for pediatric HSPN patients are mainly graded according to proliferative changes in the kidneys, such as mesangial proliferation and crescent formation. These standards ignore chronic lesions, such as tubulointerstitial damage, glomerulosclerosis and fibrosis. However, in practice, the chronic level of pathological changes in adult HSPN is greater than that in children and is a strong prognostic factor.[21] The application of the ISKDC grading in adults has many limitations. In our study, the CI and AI[16] scores included more

indicators of renal pathological changes and thus comprehensively reflected the pathological severity, but a larger sample size is still required to verify their clinical significance. A recent study has found that the Oxford classification of IgA nephropathy can be used to predict the long-term outcomes of HSPN patients.[25] The establishment of a standard of pathological grading for adult HSPN is urgently required to evaluate disease severity and to better assist in guidingpatient treatment.

Hyperuricemia may be involved in HSPN progression in adults. Recent studies[26-29] have shown that hyperuricemia might be associated with glomerular sclerosis and tubulointerstitial fibrosis and that it might induce diabetic nephropathy, affect the progression of chronic kidney disease, and promote the progression of IgA nephropathy as an independent risk factor. Henoch-Schönlein purpura nephritis shows some similarities to IgA nephropathy in terms of its etiology and pathology. In this study, the serum uric acid level was found to be positively correlated with the pathological grade and the AI and CI scores, suggesting that hyperuricemia may be involved in HSPN's progression. The relationship between serum uric acid levels and HSPN will be clarified in our future studies.

There are several limitations to our study. First, it is a single-center retrospective study. Second, long-term follow-ups to assess prognostic accuracy were not conducted, and these will be performedin our next study. Aprospective clinical study with a larger sample size must be performed to better understand the disease characteristics of adult HSPN.

CONCLUSIONS

Renal biopsy is the gold standard for assessing renal impairment in HSPN patients. However, as renal biopsy is an invasive examination, it may increase the mental and physical burdens on patients; therefore, it is necessary to assess the degree of renal pathological damage using a noninvasive method. In this study, kidney failure and the 24-hour urinary protein, serum uric acid, cystatin C, and β2-microglobulin levels were positively correlated with the pathological grade and activity. The patients with old age, kidney failure, and hyperuricemia had a high CI score and a poor prognosis. The clinical characteristics of the adult HSPN patients showed some correlations with the severity of the renal pathology. Therefore, predicting renal pathological changes based on clinical manifestations is feasible in adult HSPN patients.

CONFLICT OF INTEREST

None declared.

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