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Original Article

Higher pathological grading is associated with unfavorable outcome of Henoch-Schonlein purpura nephritis in children

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Abstract: Purpose: In order to understand the prognosis and provide reasonable diagnosis for Henoch-Schonlein purpura nephritis (HSPN) in children, we collected the clinical, pathological data and analyzed the relationship between the variables and outcomes to elicit the importance of pathologicalgrading in HSPN treatment. Methods: Analyses of 159 cases of clinical and pathological data of HSPN in children were conducted retrospectively. Prognosis of this disease was compared with both clinical and pathological variables. Results: As pathological characteristics, according to the international standards, 71 cases of level II (44.7%), 76 cases of level III (47.8%), 6 cases of level I, and 6 others were classified. As the follow-up results, 99 cases of normal (62.3%), 49 cases of mild abnormal urine (30.8%), 6 cases of active kidney diseases (3.8%), and 5 cases of renal insufficiency (3.1%) were identified. There was a correlation between the frequency of skin purpura and pathological grading ($P<0.05$). The more occurred time of purpura was related to the relatively severer degree of pathological lesion. Clinical classification was associated with pathological grading by tested with Qmh ($P<0.01$). More importantly, we found that higher pathological grading was associated with unfavorable outcome of Henoch-Schonlein purpura nephritis in children ($P<0.01$). Conclusion: The higher pathological grading was associated with unfavorable outcome for prognosis of HSPN in Children.

Keywords: HSPN, clinical, pathology, prognosis

Introduction

Henoch-Schonlein Purpura is one of the most common vasculitides in the childhood [1]. The renal damage resulted from anaphylactoid purpura is called Henoch-Schonlein purpura nephritis (HSPN), which is the main factor that influences its prognosis. HSPN was reported that about 30%~50% of children patients suffered renal damage that was the common secondary glomerular disease [2, 3]. The survey conducted by 105 hospitals in 1982 showed that HSPN possessed 8% of urologic diseases which ranked the third disease in the inpatient department of pediatrics [4]. Recently, the morbidity of HSPN was rising rapidly with the increasing of morbidity of anaphylactoid purpura. The hospitalized cases in the Children's Hospital of Zhejiang University School of Medicine were increased from 40 cases in 1999 to 140 cases in 2004, which percentage of hospitalized cases in the nephrology department was rapidly increased from 7.9% to 17.6%. The case of renal puncture due to HSPN was 29.3% of the total cases, and 1-5% of renal puncture might develop end-stage renal failure as 14% of end-stage renal failure among children [5].

In order to further understand the clinic, pathology and prognosis of HSPN in children, the total of the 159 cases of HSPN diagnosed by the Children's Hospital, Zhejiang University School of Medicine, were performed with retrospective analysis. The clinical, pathological characteristics and the relationship between all variables and prognosis were studied. The long-term follow-up and the realization of prognosis would be important for the future diagnosis and treatment.

Patients and methods

Study population

The subjects in this study were the children patients who were hospitalized and were clini-

cally diagnosed as HSPN in nephrology department of the Children's Hospital, Zhejiang University School of Medicine from January, 1992 to February, 2006 without the treatment of mycophenolate mofetil (MMF) and cyclophosphamide. All of the cases were diagnosed as HSPN via to renal biopsy. The diagnostic criteria of HSPN were included existing hematuresis and (or) albuminuria in the course of the disease (the majority within 6 months), IgA depositing in mesangial area of immunofluorescence examination in nephridial tissues; whereas systemic lupus erythematosus and chronic liver disease had been excluded.

Collection of demographic and clinical data

Clinical and pathologicaldata were collected and analyzed retrospectively with follow-up. The main clinical indexes included gender, age, course of the disease, the time between purpura and abnormal urine, recurrent purpura, blood pressure, 24-hour urine protein quantitation, level of serum IgA, clinical type. Urinalysis, urine protein quantitation, serum creatinine, and urea were examined regularly during the follow-up.

Renal biopsy and pathological examination of nephridial tissue

Intravenous pyelogram (IVP)-electrical positioning method with liposuction of kidney tissue method was performed prior to August, 2000. After that, percutaneous needling biopsy of kidney under B ultrasound guidance was employed by using true-cut automatic puncture needle to collect nephridial tissues. Nephridial tissues with 2-3 μm were embedded by paraffin; then dyed with routine HE, PAS, PASM and Masson staining. Pathologic examination was taken under light microscope; IgA, IgG, IgM, complement C3, C4, C1q and fibrinogen were taken by direct immunofluorescence examination.

Clinical types and distribution

According to the clinical manifestation [6], HSPN can be divided into six types, including (1) simple hematuria or simple urinary protein; (2) hematuria and albuminuria; (3) acute nephritis; (4) nephritic syndrome; (5) rapidly progressive glomerulonephritis; (6) chronic nephritic nephritis.

Pathological diagnosis and grading standards

By light microscope: divided into 6 types, according to the criteria by ISKDC.

By immunofluorescence and immuno-pathogenesis type (divided into 4 types , according to the immune complex depositing in glomerulus): (1) IgA type, simple IgA deposition; (2) IgA, G type, IgA+IgG deposition; (3) IgA, M type, IgA+IgM deposition; (4) IgA, G, M type, IgA+IgM+IgG deposition.

Therapeutic regimen

According to the clinical manifestation of the cases, combined with pathologic changes, therapies of grading and coherence were employed.

Identification of prognosis

Four types of HSPN children were identified according to Counahan criteria [7] in ascending order by clinical symptoms into four types of A, B, C, and D for the judgment of prognosis.

Type A-normality: physical examination, urinalysis and renal function of children patients were all normal; Type B-mild abnormal urine: physical examination and renal function were normal, but there was microhematuria or (and) albuminuria was less than 1 g/24 h; Type C-active kidney disease: albuminuria was equal to or greater than 1 g/24 h, with hypertension equal to or greater than 1.0 $ml \cdot s^{-1}/1.73\ m^2$; Type D-renal insufficiency: active kidney disease with GFR less than 1.0 $ml \cdot s^{-1}/1.73\ m^2$, or death.

Statistical analysis

The major clinical measurement data analyzed in this study were denoted by $\bar{x} \pm S$. The classified enumeration data were used by Qmh; and measurement data were tested correlatively by Spearman. The continuous variables were denoted by mean and standard deviation. The classified variables were denoted by frequency and percentage. As for the continuous variable, the comparison among many groups accorded with normal distribution was analyzed by variance; and the comparison between two groups was tested by t-test; the comparison among many groups incompatible with normal distribu-

Table 1A. Characteristics of study population

Variable	n = 159
Age (yrs), mean ± sd.	9.38±2.58
Male, n (%)	102 (64.15)
Date to renal biopsy, n (%)	87.53±142.03
Abnormal Urinary to renal biopsy, n (%)	70.19±140.63
IGA (g/L), mean ± sd.	1.86±0.80
IGM (g/L), mean ± sd.	1.44±0.69
Date to Abnormal Urinary, n (%)	
1 wk	89 (55.97)
1 wk-1 mon	56 (35.22)
1 mon-3 mon	11 (6.92)
>3 mon	3 (1.89)
C3, n (%)	
-	31 (19.5)
+	56 (35.22)
++	69 (43.4)
+++	3 (1.89)
Tubules type, n (%)	
+	120 (75.47)
++	32 (20.13)
+++	6 (3.77)
++++	1 (0.63)
Stomach pain, n (%)	74 (46.54)
Gastrointestinal bleeding, n (%)	19 (11.95)
Repeat Rash, n (%)	109 (68.55)
C3 (g/L), mean ± sd.	1.08±0.32
Clinical types, n (%)	
Simple hematuria or simple urinary protein	4 (2.52)
Hematuria and albuminuria	74 (46.54)
Acute nephritis	10 (6.29)
Nephrotic syndrome	70 (44.03)
Rapidly progressive glomerulonephritis	1 (0.63)
Follow-up of renal function, n (%)	
Normal	99 (62.26)
Mild urinary abnormalities	49 (30.82)
Activities kidney disease	6 (3.77)
Renal insufficiency	5 (3.14)

tion was tested by K-W, and two groups was tested by Wilcoxon two-sample test. The classified variables were tested by chi-square or fisher test. Risk factors of prognosis were analyzed by univariate logistic regression analysis and stepwise regression of multivariate regression model. *P* values for putting into and taking out of the model from stepwise regression analysis variables were set as 0.1. The entered variables for the model included patient demographics, clinical characteristics, and pathological features variables.

Results

Study population

Without the treatment of tripterygium glycoside and cyclophosphamide, total 159 cases of children patients were hospitalized and clinically diagnosed as HSPN in nephrology department of the Children's Hospital, Zhejiang University School of Medicine from January, 1992 to February, 2006 based on renal biopsy. Among them, there were 102 males and 57 females (ratio of 1.79:1) who were aged between 4 and 16 with average age of 9.38±2.58 yrs.

Clinical and pathological characteristics of study population

Among the 159 cases of HSPN, 89 cases (56%) had abnormal urine in the first week of illness, 56 cases (35.2%) were between the first week to first month, and 1 case was over six months. Renal puncture was performed in the majority of them (87 cases, 54.7%) in the first month of abnormal urine. 109 cases (68.6%) had a breakout of rashes repeatedly. 76 cases (47.8%) had arthralgia, and 74 cases (46.5%) had a history of abdominal pain. In the clinical classification, there were 74 cases of hematuria and albuminuria, which accounted for 46.6%; 70 cases of nephrotic syndrome, 44.0%; 10 cases of acute nephritis, 6.3%. Others were 4 cases of simple hematuria or simple urinary protein and one case of rapidly progressive glomerulonephritis (**Table 1A** and **1B**).

Pathological characteristics of study population

Observation under optical microscope: Basic glomerular lesions were identified with the different degrees of mesangial cell proliferation and increased mesangial matrixes, which could be divided into "focal" and "diffuse" two categories, including the formation of crescent or segmental lesions (induration, synechia, thrombus and necrosis). According to the ISKDC, the

Table 1B. Pathological characteristics clinical types

Variable	Nephrotic syndrome	Hematuria and albuminuria	Acute nephritis	*P*
	n = 70	n = 74	n = 10	
IGA (g/L), mean ± sd.	1.78±0.74	1.92±0.83	1.91±0.94	0.663
IGM (g/L), mean ± sd.	1.43±0.77	1.46±0.64	1.36±0.50	0.832
C3 (g/L), mean ± sd.	1.11±0.32	1.09±0.29	0.82±0.40a,b	0.021
Pathological				
I-II	22 (31.43)	52 (66.67)a	3 (27.27)b	
III-V	48 (68.57)	26 (33.33)	8 (72.73)	
C3, n (%)				0.589
-	13 (18.57)	17 (21.79)	1 (9.09)	
+	57 (81.43)	61 (78.21)	10 (90.91)	
FIB, n (%)				0.214
-	40 (57.14)	42 (53.85)	9 (81.82)	
+	30 (42.86)	36 (46.15)	2 (18.18)	
Immunization, n (%)				0.546
IgA	17 (24.29)	26 (33.33)	2 (18.18)	
IgA+IgG	13 (18.57)	7 (8.97)	1 (9.09)	
IgA+IgM	24 (34.29)	25 (32.05)	4 (36.36)	
IgA+IgM+IgG	16 (22.86)	20 (25.64)	4 (36.36)	
Tubules type, n (%)				0.903
+	21 (30.00)	25 (32.05)	4 (36.36)	
>++	49 (70.00)	53 (67.95)	7 (63.64)	
Follow-up of renal function, n (%)				<.001
Normal	29 (41.43)	66 (84.62)a	4 (36.36)	
Abnormal	41 (58.57)	12 (15.38)	7 (63.64)	

a: Compared with nephrotic syndrome P<0.05. b: Compared with hematuria and albuminuria P<0.05.

Table 2. Pathological characteristics of study population

Classification of ISKDC	Number	Percentage (%)
Level I	6	3.8
Level IIa	28	17.6
Level IIb	43	27.1
Level IIIa	23	14.5
Level IIIb	53	33.3
Level IVa	1	0.6
Level IVb	4	2.5
Level V	1	0.6

majorities were 71 cases of level II (44.7%, 28 cases of level IIa and 43 cases of level IIb) and 76 cases of level III (47.8%, 23 cases of IIIa and 53 cases of IIIb). And the others were six cases of level I, 5 cases of level IV and 1 case of level V (**Table 2**).

Immunofluorescence examination: Main characteristics indicated IgA deposition which was mainly distributed in mesangial area and capillary walls as affected in different degree. Depositions of immune globulin (IgG and IgM) and properdin (C3, C1q and C4) were also found. Simplified IgA, IgA+IgM and IgA+IgM+IgG were accounted for respectively 45 cases (28.3%), 53 cases (33.3%), and 40 cases (25.2%). However, there were only 21 cases (13.2%) of IgA+IgG. 128 cases (80.5%) had C3 deposition and 68 cases (42.8%) had Fib deposition; while C4 (1 case) and C1q (1 case) deposition were extremely rare (**Table 3**).

Detection under electron microscope: Depositions of electron dense granules were found in the mesentery and under the blood vessel endothelium, while a few depositions were shown under the tunica adventitia vasorum. Electron dense granules which were relatively common in the both sides of glomerular basement membrane (GBM) were related to histological classification. According to immunoelectron microscope, the distribution of electron dense granules and reaction product of IgA specificity were consistent with each other, which showed that electron dense granules were immune complexes consisted mainly from IgA.

Correlations between the types of immune deposits and pathological grading: According to the degree of pathological lesion, HSPN were divided into three groups: mild lesion (level

Table 3. Types of immunopathogenesis

Immunization types	Number	Percentage (%)
IgA	45	28.3
IgA+IgG	21	13.2
IgA+IgM	53	33.3
IgA+IgM+IgG	40	25.2
With C3 deposition	128	80.5
With Fib deposition	68	42.8
With C4 deposition	1	0.6
With C1q deposition	1	0.6

Table 4. Correlation analysis between types of immune deposits and pathological grading

Immunization types	Pathological types (level ISKDC)			Value Qmh	*P*
	I-II	III	IV-V		
IgA	25	19	1	1.493	0.68
IgA+IgG	11	8	2		
IgA+IgM	22	31	0		
IgA+IgM+IgG	19	18	3		

Table 5. Correlation analysis between C3 deposition of pathological tissues and pathological types

C3 deposition of pathological tissues	Pathological types (level ISKDC)			Qmh	*P*
	I-II	III	IV-V		
Non-depositional	16	13	2	0.003	0.95
Depositional	61	63	4		

ISKDC I-II), relatively severe lesion (level ISKDC III) and severe lesion (level ISKDC IV-V). The correlation between the grading, types of immune deposits, and C3 deposition were analyzed by Qmh test (**Tables 4** and **5**). No correlations were found between types of immune deposits and pathological grading (value Qmh of 1.493, *P*>0.05) and between C3 deposition of pathological tissues and pathological grading (value Qmh of 0.003, *P*>0.05).

Association of clinical classifications and pathology

The relationship between clinic types and pathological grading: There was no correlations between pathological grading and gender, or stomachache, or the time from paroxysm to abnormal urine (P>0.05). However, there was a correlation between the frequency of skin purpura and pathological grading (P<0.05). The more occurred time of purpura was related to the relatively severer degree of pathological lesion. More importantly, the clinical classification was associated with pathological grading by tested with Qmh (P<0.01, **Tables 6** and **7**).

The relationship between pathological grading and ages, serum IgA and level of C3: The relationships between pathological grading and ages, or serum IgA, or the level of C3 were analyzed with Spearman correlation test (**Table 8**). There was no correlations between pathological grading and ages, serum IgA and level of C3 (P>0.05).

Effect of pathological grading on outcomes of HSPN children patients

According to the clinic and pathology, 159 cases of HSPN children patients were treated with clinical classifications and pathological-grading. In the follow-up on a regular basis, the time limit was from 6 months to 14 years. 137 cases (86.2%) were more than 1 year, 113 cases (71.1%) were more than 2 years. By the follow-up, the results were shown that A: 99 cases with normality accounted for 62.3%; B: 49 cases with mild abnormal urine accounted for 30.8%; C: 6 cases with active kidney diseases accounted for 3.8%; D: 5 cases with renal insufficiency accounted for 3.1%. More importantly, we found that higher pathological grading was associated with unfavorable outcome of Henoch-Schonlein purpura nephritis in children (P<0.01, **Table 9**). The analysis of risk factors of abnormal renal function in the follow-up was seen in Table S1.

Discussion

HSPN was classified with a variety of clinical symptoms which were mostly shown as hematuria and albuminuria and nephrotic syndrome, and related to the realization of indications of renal puncture. Some children patients with simple hematuria were not treated with renal puncture due to less severe clinical manifestations [8, 9]. With regard to the prognostic factors, a number of factors have been suggested including nephrotic syndrome, hypertension, severe renal injury, high renal accumulation of activated macrophage, and alpha-smooth muscle actin [10]. Haas demonstrated that 25% of

Table 6. Correlation analysis between pathological grading and gender, stomachache, frequency of purpura and the time from morbidity to abnormal urine

Pathological types	Gender (n)		Stomachache, arthralgia and alimentary tract hemorrhage (n)		Frequency of skin purpura (n)		Time between morbidity and abnormal urine (n)			
	Male	Female	No	Yes	Once	Multiple times	<1 week	<1 month	<3 months	>3 months
I-II	50	27	29	48	31	46	46	26	4	1
III	51	25	22	54	18	58	40	27	7	2
IV-V	1	5	1	5	1	5	3	3	0	0
Qmh	1.0043		2.0110		5.2906		0.9122			
P	0.3163		0.1562		0.0214		0.3395			

Table 7. Correlation analysis between clinical types and pathological grading

Clinical classification	Pathological types (n)			Qmh	*P*
	I-II	III	IV-V		
Simple hematuria or simple urinary protein	4	0	0	25.1658	0.0001
Hematuria and albuminuria	48	26	0		
Acute nephritis	3	7	0		
Dropsical nephritis	22	43	5		
Rapidly progressive glomerulonephritis	0	0	1		

children biopsied for HSPN had severe outcomes including end-stage renal failure, in correlation with the ISKDC grades of renal pathology damage. These data indicate that children with HSPN have to be carefully followed, since some cases can have a catastrophic evolution [11, 12]. In addition, the data were shown that 91.2% of cases had urinary abnormalities within the first month of rashes. Huang et al [13] indicated that HSPN that appeared within four weeks of course was accounted for 83.3% and within three months accounted for 97.9%, which were similar to Saulsbbury et al [14]. Therefore, in order to find early stage, regular urinalysis could be performed on HSPN children patients before the six months of course.

There existed differences from our findings, which might be related to the realization of source of case and indications of renal puncture. Pathological types of tubular-interstitial indicated that level + (75.5%), followed by level ++ of 20.1%. According to the correlation analysis between pathological types of tubular-interstitial and ISKDC grading, the extent of damage of tubular-interstitial was consistent with that of glomerulus. The development of glomerulopathy was related not only to glomerular lesions, but even closely to the degree of kidney tubules and interstitial pathological changes. Existed lesions in glomerulus and kidney tubules were found at the same time in the majority of cases. Basic pathological changes were paralleled to each other, which was related to clinical manifestation, and indicated a positive correlation between minor glomerular abnormalities and the degree of renal tubular acidosis. Immunophenotyping consisted of type IgA+IgM (33.3%), followed by type simple IgA and type IgA+IgM+IgG with respectively 28.3% and 25.2%. Qin et al [15] reported that with 20 HSPN cases, type IgA+IgG with 38% was more common, followed by type IgA+IgM and type IgA+IgM+IgG both with 19%, which was related to regions and the realization of renal puncture indications. Compared with the proportion of simple type IgA, the data also showed type IgA+IgM+IgG had an increasing tendency in pathological grading. However, statistical results indicated that there was no obvious correlation between types of immunopathogenesis and pathological grading, which might be related with some factors. There were also 80.5% of C3 depositions but with a relative lack of C1q and C4 (0.6%), which was similar to the reports by Rieu et al [16]. Complement system played a role in the course of renal damage, which activation was acquired by alternative pathway. Kumada et al [17] reported that C3 depositions affected clinical manifestation pathologically and positive C3 depositions had long-duration and severe albuminuria. The data had analyzed the relationship between C3 depositions and pathological types, which indi-

Table 8. Correlation analysis between pathological grading and ages, serum IgA level and serum C3 level

Items	ISKDC I-II	ISKDC III	ISKDC IV-V	correlation coefficient of Spearman	*P*
Age (years old)	9.52±2.64	9.14±2.35	10.67±4.27	-0.04456	0.5770
serum IgA level (g/L)	1.91±0.68	1.83±0.76	1.80±0.52	-0.0882	0.2689
serum C3 level (g/L)	1.19±0.27	1.08±0.30	1.11±0.21	-0.1531	0.0541

Table 9. Relationship between prognosis and the degree of pathological lesion

Types of follow-up results	Pathological types			Qmh	*P*
	I-II	III	IV-V		
A	71	28	0	63.2023	0.0001
B	6	42	1		
C	0	3	3		
D	0	3	2		

cated that there was no correlation between them. Therefore, since it wasnot consistent with the report of Kumada K, further study was also needed.

Zhang et al [18] reported that there were 16 normal cases in renal biopsy other than in urine routine examination, which had typical symptoms of anaphylactoid purpuraas skin purpura. And 9 cases had level III and 1 case hah level IV in the pathological lesion of liver, which showed that pathological lesion of liver was not absolutely paralleled to clinical manifestation. Due to some concerns and renal puncture, renal puncture was not performed in HSPN patients whose urine routine and renal functions were normal. The correlation between pathological grading and ages (yrs), serum IgA and level of C3, tested by Spearman interrelated test, showed no relationships were found.

According to the clinical manifestations, combined with pathologic changes, HSPN children patients could be treated with pathologic grading treatment. The majority had better prognosis after treated with general symptomatic, immunoregulation, glycosides of triptericium-wilfordiihook (GTW), Adrenocorticotropic hormone, cyclophosphamide. We followed up all cases from 6 months to 14 years. As a result, 93.1% turned out normal clinically or mild abnormal urine, 3.8% turned out active kidney disease and 3.1% turned out renal insufficiency; 3 cases were performed kidney transplant. The follow-up results were shown that there were 5 cases turning out renal insufficiency, in which 3 cases were at level III and 2 cases were at level IV-V; there were 6 cases turning out active kidney disease, in which 3 cases were pathologically at level III and 3 cases were at level IV-V. The follow-up indicated that 5 cases of level IV-V, 1 case of level B, 3 cases of level C and 2 cases of level D. The statistical analysis were shown that there was a correlation between pathological grading and prognosis (P<0.01). Therefore, the level III or above (especially level IV-V) were needed an active treatment and long-term follow-up. Goldstein et al [19] followed 78 cases up for 23.4 years (19-35.1 years) and performed surveys respectively in 1971, 1976 and 1990. Level C+D had 14 cases in 1971 and 22 cases in 1990 accounted for 28%. Among the 12 cases which formation of crescent was appeared in over 50% of glomerulus, 7 cases (58%) turned out unfavourable prognosis. According to the statistical report [19], among the 11-year cumulative survival rates of 116 HSPN cases, exacerbation was appeared within 5 years to develop renal insufficiency, which needed 5-year observation. Therefore, HSPN children patients needed long-term follow-up, especially for those who had severer clinical and pathological manifestations. In a conclusion, the higher pathological grading was associated with unfavorable prognosis of HSPN in children.

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Disclosure of conflict of interest

None.

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Table S1. The analysis of risk factors of abnormal renal function in the follow-up

Factors	Unadjusted*		After adjusting the multi-factor**	
	OR (95% CI)	*P*	OR (95% CI)	*P*
IgA, unit = 1	1.20 (0.80, 1.79)	0.378	2.08 (1.15, 3.78)	0.016
Pathological grading		<0.001		<0.001
I-II	1		1	
III-V	22.82 (8.83, 59.01)		23.94 (8.07, 71.08)	
Clinical types		<0.001		<0.001
Hematuria and albuminuria	1		1	
Acute nephritis	9.62 (2.44, 38.02)		7.88 (1.42, 43.76)	
Dropsical nephritis	7.78 (3.57, 16.92)		7.22 (2.69, 19.40)	

*Univariate logistic regression analysis, **multivariable logistic regression analysis.