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Analysis on kidney injury-related clinical risk factors and evaluation on the therapeutic effects of hemoperfusion in children with Henoch-Schonlein purpura

D.-Q. MA[1], Y. LI[2], Z.-G. HAN[3], M. ZHENG[4], N. XU[5], X.-J. FAN[6]

[1]Department of Pediatrics, Yantaishan Hospital, Yantai, Shandong, China
[2]Department of Internal Medicine, Rizhao People's Hospital, Rizhao Shandong, China
[3]Blood Purification Room, Zhangqiu District Hospital of Traditional Chinese Medicine, Jinan, Shandong, China
[4]Department of Internal Medicine, People's Hospital of Zhangqiu, Jinan, Shandong, China
[5]Department of Radiology, People's Hospital of Zhangqiu, Jinan, Shandong, China
[6]Experimental Diagnostic Medical Center, Jinan Central Hospital Affiliated to Shandong University, Jinan, Shandong, China

Abstract. – OBJECTIVE: To investigate risk factors related to kidney injury in children with Henoch-Schonlein purpura (HSP) and to study the therapeutic effects of hemoperfusion (HP) on kidney injury in HSP children, providing clinical evidence for early prevention and treatment of HSP.

PATIENTS AND METHODS: Children who suffered from HSP for the first time were selected as study objects and they were followed up for 12 months. Single factor analysis and multi-factor Logistic regression analysis were performed for children's demographic characteristics (age, gender), clinical manifestations (rash duration time, rash recurrence times, digestive tract hemorrhage, abdominal pain, arthralgia, HSP recurrence) and laboratory indexes (peripheral blood WBC, PLT, ESR, CRP, serum IgG, serum IgA, IgM, serum C3, serum C4, TC, TG, HDL, LDL). Meanwhile, participants were divided into treatment group (HP treatment) and control group, and the protective effects of HP on renal function of HSP children were discussed.

RESULTS: Single factor analysis indicated age ≥ 6 years, rash recurrence ≥ 3 times, rash duration time ≥ 1 month, digestive tract hemorrhage, peripheral blood PLT, WBC, serum TC and serum LDL levels had statistically significant differences between the two groups. Multi-factor Logistic regression analysis indicated rash recurrence ≥ 3 times, digestive tract hemorrhage, decline of peripheral blood PLT count, and increases of serum TC and LDL were closely related to kidney injury of HSP children. After discharge, kidney injury comparison between treatment group and control group in follow-up had a statistical difference.

CONCLUSIONS: Rash recurrence ≥ 3 times, digestive tract hemorrhage, decline in peripheral blood PLT count, increases of serum TC and LDL, are risk factors of kidney injury in HSP children. HP can protect renal function of HSP children.

Key Words:
Henoch-Schonlein purpura (HSP), Children, Kidney injury, Risk factors, Hemoperfusion.

Introduction

Henoch-Schonlein purpura (HSP) is one of the common systemic vasculitis in childhood, characterized with IgA-dominated immunoglobulin complexes depositing on small vascular walls[1]. It can occur at every age and is the most common in children, with male and female ratio of 1.4:1[2]. Its clinical features are non-thrombocytopenic purpura, arthritis, arthralgia, abdominal pain, gastrointestinal bleeding and kidney injury, and there have been reports that muscle damage and central nervous system damage may exist[3-6]. HSP in children is self-limited and most of them have good prognosis, but the duration of disease courses are different and their prognosis is different. Recurrent HSP has a long course and its repeated attack is easy to be followed by kidney injury, and about 1.5-10% patients eventually develop into chronic renal failure[7]. However, kidney's involve-

Corresponding Author: Xiujie Fan, MD; e-mail: slyymwz@163.com

ment degree and treatment outcome are the major factors determining the prognosis of HSP children. Therefore, research on kidney injury-related clinical risk factors will be crucial to the early prevention and treatment of Henoch-Schonlein purpura nephritis (HSPN).

In recent years, hemoperfusion (HP) has become a trend of present clinic in treating severe HSPN. There have been research reports showing that HP can more obviously remit children's clinical symptoms at acute stage, such as abdominal pain, digestive tract hemorrhage, joint swelling and pain, and speed up the recession of skin purpura, but it has not yet reached a consensus on its protective effects on kidney of HSP children in academia[8-10]. However, it has not yet reached a consensus on its protective effects on kidney of HSP children in academia.

To sum up, understanding HSP recurrence-related risk factors in children sufficiently can contribute to clinical early diagnosis, intervention and treatment. Thus, reducing HSP recurrence rate in children, and improving children's kidney injury and prognosis. At present, the research on risk factors of HSP recurrence in children is insufficient. In this work, we analyzed clinical data of HSP children and summarized the related risk factors that affected HSP recurrence in children, to provide theoretical basis for early preventing HSP recurrence. At the same time, the therapeutic effects of HP on kidney injury of HSP children were explored to provide clinical basis for HSP treatment.

Patients and Methods

Patients

Children hospitalized in Jinan Central Hospital Affiliated to Shandong University (Shandong, China) and diagnosed with HSP for the first time from January 2015 to December 2016, were selected as study objects for analysis. There were 264 children, including 14 cases lost to follow-up, who were removed, and 250 children who conformed to diagnosis standard were selected as study objects. This study was approved by the Ethics Committee of Jinan Central Hospital Affiliated to Shandong University. Signed written informed consents were obtained from all participants' parents before the study.

Definition of Observation Indexes

(1) Definition of HSP recurrence: HSP characteristic manifestations occurred again after at least 1 month since the symptoms of children diagnosed with HSP faded away; (2) rash recurrence: purpura-like rash recurred group by group after the last rash disappeared; (3) kidney involvement: urine specimens of different days were detected with hematemesis and (or) proteinuria, which was defined as kidney involvement, excluding hematemesis and (or) proteinuria caused by external and urinary system infections (routine urine examination: WBC $<5 \cdot$HP-1, urine WBC $<25 \cdot \mu L^{-1}$ or urine culture was negative).

Grouping of Treatment Measures

(1) Treatment group: there were 72 children who accorded with classification standard of HSP children and whose guardians signed written consent of hemoperfusion, and these children received hemoperfusion and general treatment. (2) Control group: there were 178 children, who accorded with classification standard of HSP children but whose guardians refused to sign written consent of hemoperfusion, and these children just received general treatment.

Follow-up

(1) The period of the follow-up: 12 months of follow-up from the date when the selected children were diagnosed with HSP (in 1 month, 3 months, 6 months and 12 months since the initial date of follow-up). (2) The methods of the follow-up: follow-up could be made through return visit records or telephone. (3) The contents of the follow-up: rash recurrence of HSP children, duration and recurrence of rash, and blood examination results of our hospital or local hospitals.

Methods

(1) Analysis on clinical risk factors: clinical risk factors related to kidney injury in HSP children were selected via literature consulting, including demographic factors: gender and age; clinical manifestations: duration of rash, rash recurrence times, joint swelling and pain, abdominal pain, digestive tract hemorrhage and HSP recurrence; laboratory indexes: white blood cells (WBC), platelets (Plt), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum IgG, IgA, IgM, serum C3, serum C4 level, TC, TG, HDL and LDL in the initial peripheral blood of hospitalized children. Through follow-up of the HSP children included into research, single factor analysis of each

risk factor was performed first, and then logistic regression analysis of variables, which had statistical significance, was performed, thus factors of kidney injury of children who suffered from HSP for the first time were found out.

(2) Analysis on HP therapeutic effects: through follow-up results of treatment group/control group and according to definition of kidney injury, study objects in each group were divided into kidney injury group/non-kidney injury group, and X^2 test of fourfold table was used to compare whether prevalence rate of kidney injury has statistical differences, by which to evaluate HP therapeutic effects.

Statistical Analysis

All statistics were performed using SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). *t*-test and X^2 test were performed for the comparison of the significant difference between groups. Multiple Logistic regression analysis was used to evaluate the relationship between the parameters of HSP kidney injury and predictor factors. $p<0.05$ suggested statistical significance.

Results

General Data

A total of 264 children who suffered from HSP for the first time were included in this research, including 153 males (57.95%) and 111 females (42.05%), with male and female ratio of about 1.38:1. The smallest onset age was 2 years and the oldest was 14 years, with an average onset age of (7.81±2.63) years. 250 children finished follow-up and 14 children were lost to follow-up, and rate of losing follow-up was 5.30%. There were 103 children who had kidney injury in 250 HSP children included into analysis, and prevalence rate was 41.20%. When age and gender in two groups were compared in pairs, all *p*-values >0.05 and differences were not statistically significant (Table I).

Clinical Features

All included HSP children had symptom of rash purpura, among which there were 59 children whose rash duration time ≤ 14 days, 113 children were 15-21 days, 53 children were 22-29 days and 39 children ≥ 1 month; there were 186 children whose rash recurrence times ≤ 2 times and 78 children ≥ 3 times; there were 116 children (43.94%) who had joint symptoms, for example joint swelling and pain; there were 170 children (64.39%) who were accompanied by abdominal pain; there were 42 children (15.91%) who had digestive tract hemorrhage (Table I).

Table I. Baseline characteristics of included patients.

	N (%)
Male	153 (57.95)
Age (≥ 6 y)	197 (74.62)
Rash duration ≤ 14 d	59 (22.35)
Rash duration 15-21 d	113 (42.80)
Rash duration 22-29 d	53 (22.35)
Rash duration ≥ 1 m	39 (14.77)
Recurrence of rash ≥ 3 times	78 (29.55)
Recurrence of HSP	105 (39.78)
Joint symptoms	116 (43.94)
Abdominal pain	170 (64.39)
Digestive tract hemorrhage	42 (15.91)

Note: Abbreviation: HSP: Henoch-Schonlein purpura.

Single Factor Analysis on Kidney Injury Risk Factors

There were statistically significant differences in age ≥ 6 years, rash recurrence ≥ 3 times, digestive tract hemorrhage, peripheral blood PLT, WBC, serum TC and serum LDL level of two groups ($p<0.05$, Table II); there were no differences in gender, joint symptoms, abdominal pain, HSP recurrence, incidence rates of peripheral blood IgA, IgG, IgM, C3, C4, TG, HDL level, incidence rates of ESR>18 mg/L and CRP>10 mg/L of two groups ($p>0.05$, Table II).

Multi-factor Logistic Regression Analysis on Kidney Injury Risk Factors

Rash recurrence ≥ 3 times, digestive tract hemorrhage, decline of peripheral blood PLT count, increase of serum TC and increase of serum LDL level were risk factors of kidney injury in HSP children ($p<0.05$, Table III).

Evaluation of HP Therapeutic Effects

Kidney injury occurrence during 1 year of follow-up after children in treatment group and control group discharged from hospital: there were 18 cases (16.07%) in treatment group and 63 cases (45.65%) in control group, and kidney injury comparison between control group and treatment group when the two groups were compared, had statistical differences ($p<0.05$, Table IV).

Table II. Single factor analysis of kidney injury risk factors.

Factor	HSPN (n=103)	HSP (n=147)	t / c2	p
Age ≥ 6 years	83	114	2.355	0.027
Rash duration time ≥ 1 month	26	13	8.174	0.031
Rash recurrence ≥3 times	54	24	9.295	0.000
Digestive tract hemorrhage	23	19	11.857	0.000
WBC	14.1±5.7	8.6±4.5	5.861	0.000
Plt	282.7±55.4	374.5±60.2	-7.038	0.000
TC	4.82±1.26	3.65±1.19	3.486	0.023
LDL	3.25±1.09	2.29±0.83	4.017	0.000

Note: HSP: Henoch-Schonlein purpura; HSPN: Henoch-Schonlein purpura nephritis.

Table III. Multiple Logistic regression analysis of factors related to kidney injury.

Factor	B	S.E.	Wald	p
Rash recurrence ≥ 3 times	1.669	0.375	9.766	0.001
Digestive tract hemorrhage	1.764	0.327	3.156	0.018
Decline of Plt	5.365	1.526	6.374	0.000
Increase of TC	-2.437	0.904	6.259	0.008
Increase of LDL	-2.805	0.957	7.435	0.004

Table IV. The effect evalution of kidney protection in HSP children received HP.

	HP group (n=72)	Control group (n=178)	t/χ^2	p
Male	55	135	7.619	0.502
Age (y)	8.26±3.09	7.64±2.52	3.607	0.084
Kidney injury	9	47	13.304	0.000
Increase of LDL	-2.805	0.957	7.435	0.004

Note: HSP: Henoch-Schonlein purpura; HP: hemoperfusion. $p<0.05$ suggested statistical significance.

Discussion

HSP is the most common systemic micro-vessel inflammation, dominated by system damage, such as skin damage, gastrointestinal tract damage, joint damage and kidney damage, and its incidence rate presents an increasing trend year by year[1,2]. Incidence rate of kidney injury in recurrent HSP children is higher than that in children who have HSP for the first time, and increased recurrence times can make nephritis develop into severe type from slight type in clinic classification, and the more recurrence times, the worse prognosis[7-10]. So searching for recurrence incentives actively and reducing recurrence times are very important links in treating HSP. The initial clinical manifestations and laboratory examination of HSP are close with the recurrence of HSP, and seeking for possible clinic-related factors actively can bring beneficial reference for clinical diagnosis and treatment, prevention of recurrence and determination of disease prognosis. In the past few years, hemopurification has been one of the important adjuvant treatment means for HSP in children, and there has been more literature reporting that HP has achieved satisfactory results in treating HSP, but now there still has not reached a consensus about whether HP treatment protects kidney of HSP children or not[11-13]. Through 1 year of follow-up and related statistics of children who suffered from HSP for the first time, this research analyzed the risk factors of HSP kidney injury and investigated the protective efficacy of HP on kidney.

Statistical analysis of this research found that when single factor (age ≥ 6 years) was analyzed, it was statistically significant about

whether children had kidney injury or not, but when further logistic regression analysis was conducted, it had no statistical differences in two groups about whether children have kidney injury or not. This suggests that age ≥ 6 years is related to the occurrence of HSP kidney injury, but it still cannot be considered as the independent risk factor of kidney injury occurrence[6]. There have been reports of different opinions in China and foreign countries about whether age can serve as the independent risk factor of kidney injury or not. There have been researches considering age ≥ 4 years, ≥ 8 years and ≥ 10 years as the independently clinical risk factor of HSP kidney injury. Kaku et al[14] studied and found that when age of onset ≥ 7 years, the chance of HSP kidney injury occurrence was greater. de Almeida et al[15] had studied 142 HSP children for 21 years and found that gender and age were not correlated to HSP kidney injury. Analysis of this research revealed that there were no differences in gender of two groups about whether kidney injury occurred in children or not, indicating gender is not the risk factor causing HSPN.

This work found that there were no differences in single factor analysis among rash recurrence ≥ 3 times and duration of rash ≥ 1 month in two groups about whether children had kidney injury, and logistic regression analysis showed that rash recurrence ≥ 3 times could be considered as the independent risk factor of kidney injury occurrence, but duration of rash ≥ 1 month was not related to the occurrence of HSP kidney injury. There have been researches finding that rash recurrence is related to HSP kidney injury, which corresponds with the results of this research, indicating repeated purpura recurrence is easy to induce micro-vessel inflammation in body, which makes immune complexes deposit and activates complement system, resulting in secondary damage to glomeruli.

Results of this work also showed that abdominal pain was not statistically significant in two groups about whether children had kidney injury or not, while digestive tract hemorrhage had differences in two groups in X^2-test of single factor and multi factor logistic regression analysis, indicating that digestive tract hemorrhage can be considered as the risk factor of HSP kidney injury occurrence. This is consistent with the results of domestic researches in which digestive tract hemorrhage is the high risk factor of HSPN. This investigation inspected joint symptoms and HSP recurrence and revealed that there were no differences in two groups in kidney injury, indicating joint symptoms and HSP recurrence are not clinical risk factors of kidney injury.

Analysis of laboratory indexes suggested that there were no differences in peripheral blood IgA, IgG, IgM, C3, C4, TG, HDL level, the occurrence rates of ESR > 18 mg/L and CRP > 10 mg/L in two groups, while peripheral blood PLT, WBC, serum TC, serum LDL level had statistically significant differences in two groups. Also, decline in peripheral blood PLT count, increase of serum TC and increase of serum LDL level were the independent risk factors of kidney injury of HSP children. This is considered to be related to PLT serum TC and LDL participating in the occurrence of vascular inflammation and activating complement system, which plays an important role in HSPN. However, its specific mechanism of action needs to be studied further.

There have been researches revealing that after HP is performed in HSP children, IgA, IL-17, TGF-β1, inflammatory media (leukotrienes, arachidonic acid, cytokines, chemotactic factors, C3a, C5a, etc.) levels and so on in peripheral blood, are detected to be decreased when compared with that in non-HP group. The mechanism of HP protecting kidney mainly may be that pathogenic components are eliminated, such as circulating immune complex and inflammatory mediators. Additionally, autoimmunity is adjusted and steady state in the body is recovered, relieving kidney injury. There were statistical differences in kidney injury of treatment group and control group in this research, indicating HP can reduce the occurrence rate of kidney injury in HSP children and protect renal function.

Conclusions

Rash recurrence ≥ 3 times, digestive tract hemorrhage, decline of peripheral blood PLT count, increase of serum TC and increase of serum LDL level are risk factors of kidney injury in HSP children. HP can protect renal function of HSP children. HSP children with high risk factors should receive treatment as soon as possible (HP can be given) and be followed up, so as to improving children's prognosis and enhance survival quality.

Conflict of interest

The authors declare no conflicts of interest.

References

1) Feng D, Huang WY, Hao S, Niu XL, Wang P, Wu Y, Zhu GH. A single-center analysis of Henoch-Schonlein purpura nephritis with nephrotic proteinuria in children. Pediatr Rheumatol Online J 2017; 15: 15.
2) Hwang JJ, Ahn J, Kim KP, Choi HI, Choi JY, Song R, Lee YA, Lee SH, Hong SJ, Yang HI. Henoch-Schonlein purpura with muscle involvement, presenting as myositis. J Clin Rheumatol 2017; 23: 60-62.
3) Lu S, Liu D, Xiao J, Cheng G, Wang X, Zhang X, Yuan W, Dou Y, Liu Z, Zhao Z. Independent association between hyperuricemia and histopathological parameters in chinese patients with Henoch-Schonlein purpura nephritis. Clin Lab 2016; 62: 2271-2275.
4) Shiari R, Tabatabaei NS, Mohebbi MM, Karimzadeh P, Javadzadeh M. Moyamoya syndrome associated with Henoch-Schonlein purpura. Iran J Child Neurol 2016; 10: 71-74.
5) Wu JJ, Zhu YT, Hu YM. Mechanism of feedback regulation of neutrophil inflammation in Henoch-Schonlein purpura. Eur Rev Med Pharmacol Sci 2016; 20: 4277-4285.
6) Zhang N, Guo PJ, Liu PL, Yang HR, Xiao J, Li XP, Huang JB, Zheng YZ. [Comparison of age-based clinical and abnormal immune parameters in patients with Henoch-Schonlein purpura]. Zhonghua Xue Ye Xue Za Zhi 2017; 38: 60-64.
7) Delbet JD, Hogan J, Aoun B, Stoica I, Salomon R, Decramer S, Brocheriou I, Deschenes G, Ulinski T. Clinical outcomes in children with Henoch-Schonlein purpura nephritis without crescents. Pediatr Nephrol 2017; 32: 1193-1199.
8) Chen JY, Mao JH. Henoch-Schonlein purpura nephritis in children: incidence, pathogenesis and management. World J Pediatr 2015; 11: 29-34.
9) Davin JC, Coppo R. Henoch-Schonlein purpura nephritis in children. Nat Rev Nephrol 2014; 10: 563-573.
10) Fu H, Mao J, Xu Y, Gu W, Zhu X, Liu A. Clinical features and outcomes of diffuse endocapillary proliferation Henoch-Schonlein purpura nephritis in children. Clinics (Sao Paulo) 2016; 71: 550-554.
11) Hamilton P, Ogundare O, Raza A, Ponnusamy A, Gorton J, Alachkar H, Choudhury J, Barratt J, Kalra PA. Long-term therapeutic plasma exchange to prevent end-stage kidney disease in adult severe resistant Henoch-Schonlein purpura nephritis. Case Rep Nephrol 2015; 2015: 269895.
12) Huang YJ, Yang XQ, Zhai WS, Ren XQ, Guo QY, Zhang X, Yang M, Yamamoto T, Sun Y, Ding Y. Clinicopathological features and prognosis of membranoproliferative-like Henoch-Schonlein purpura nephritis in children. World J Pediatr 2015; 11: 338-345.
13) Tudorache E, Azema C, Hogan J, Wannous H, Aoun B, Decramer S, Deschenes G, Ulinski T. Even mild cases of paediatric Henoch-Schonlein purpura nephritis show significant long-term proteinuria. Acta Paediatr 2015; 104: 843-848.
14) Kaku Y, Nohara K, Honda S. Renal involvement in Henoch-Schonlein purpura: a multivariate analysis of prognostic factors. Kidney Int 1998; 53: 1755-1759.
15) de Almeida DC, Donizetti-Oliveira C, Barbosa-Costa P, Origassa CS, Camara NO. In search of mechanisms associated with mesenchymal stem cell-based therapies for acute kidney injury. Clin Biochem Rev 2013; 34: 131-144.