Original Article

Iranian Journal of Immunology
https://iji.sums.ac.ir

Changes of Peripheral Blood Lymphocyte Subsets and Immune Function in Children with Henoch-Schoenlein Purpura Nephritis

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ABSTRACT

Background: Purpuric nephritis is the most common secondary glomerular disease in childhood. Its prevalence in children has been steadily rising in recent years.

Objective: To explore the characteristics and pathogenesis of changes in peripheral blood lymphocyte subsets and immune function in children with Henoch-Schonlein purpura nephritis.

Methods: The study included 104 children with Henoch-Schonlein purpura, divided into nephritis (HSPN) group (68 cases) and non-nephritis (NHSPN) group (36 cases), and 15 normal children. The rate-scatter turbidimetric method was utilized to determine the immunoglobulins IgA, IgG, IgM, C3 and C4, and the flow cytometry technique was employed to detect the levels of lymphocyte subsets including CD3+, CD4+, CD8+, CD4+/CD8+, CD19+, NK, etc.

Results: Compared with the control group, the CD3+, CD4+, CD8+ and NK cell levels of peripheral blood mononuclear cells significantly decreased ($P<0.05$), and the CD19+ level significantly elevated ($P<0.05$) in the HSPN group and the NHSPN group whereas the HSPN group had a more significant change than the NHSPN group ($P<0.05$). Compared with the control group, the serum immunoglobulin IgA and IgG of the HSPN group and the NHSPN group significantly increased, and the IgM, C3, and C4 significantly decreased ($P<0.05$); while the HSPN group had a more significant change than the NHSPN group ($P<0.05$).

Conclusion: Immune dysfunction in children with HSPN is specifically manifested as low cellular immune function, which leads to an increased secretion of inflammatory mediators, activates B cells, and further increases the secretion of immunoglobulins, leading to the occurrence of small vasculitis.

Keywords: Complement, Henoch-Schonlein Purpura, Immunoglobulin, Lymphocyte Subsets, Purpuric Nephritis

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Cite this article as:
Su QX, Jiang LJ, Chai Ja, Dou ZY, Rong ZH, Zhao X, Yu B, Wang YX, Wang XL. Changes of Peripheral Blood Lymphocyte Subsets and Immune Function in Children with Henoch-Schoenlein Purpura Nephritis. *Iran J Immunol.* 2021; 18(3):259-267, doi: 10.22034/iji.2021.89742.1964.

Received: 2021-01-12
Revised: 2021-06-30
Accepted: 2021-07-26

INTRODUCTION

Henoch-Schoenlein Purpura (HSP) is a common multi-system and multi-organ involvement vasculitis disease characterized by the deposition of immunoglobulin A (IgA) in small blood vessels in childhood (1, 2). When children with HSP have gross hematuria, microscopic hematuria and/or

proteinuria, or tubular urine and other clinical renal damage, called Henoch-Schoenlein Purpura nephritis (HSPN) and it often occurs more than 4-6 weeks after the onset of HSP (3).

The etiology and pathogenesis of HSP have not yet been fully elucidated, and the infection is currently believed to be the main factor inducing the onset of HSP (4, 5). The pre-infection of group A hemolytic streptococcus is closely related to the onset and progression of the HSP. Studies have shown that abnormalities in IgM, IgG, IgD, IgE, so on and so forth, are related to the pathogenesis of HSPN. However, there is no consistent result in the study of changes in IgM and IgG levels in children with the HSPN. The pathological mechanism of organ-specific IgA deposition is not determined yet. Research on the correlation between the immune factors and organ damage of the HSP in Chinese children has shown that organ damage is related to Th1/Th2 imbalance (6). Current research shows that the imbalance of cellular immunity may be related to the HSPN.

Gonghe et al., (7) reported that regulatory B cells in B cells could induce the activation of Treg cells and inhibit the proliferation of Th17 cells, thereby playing an immunosuppressive role, leading to the occurrence and development of the HSP. The research of Pan YX et al., (6) showed that the percentage of NK cells in children with the HSP decreased. When the children had kidney and digestive system damage, the percentage of NK cells decreased even lower. In addition, the abnormal blood coagulation function was important for the HSP (8).

At present, the HSP‘s innate and adaptive immune system is still unclear. Therefore, understanding the changes and connections between humoral and cellular immunity in children with the HSPN is important for understanding pathogenesis.

MATERIALS AND METHODS

Research Object

In this study, 104 newly-treated children with allergic Purpura were hospitalized in the Second Hospital of Hebei Medical University from April 2017 to November 2018. Based on the Guidelines for Purpura Nephritis formulated by the Nephrology Group of the Pediatrics Branch of the Chinese Medical Association in 2016, children with the HSP are divided into the nephritis (HSPN), and the non-nephritis (NHSPN) groups. Among them, 68 were NHSPN, 36 were HSPN. At the same time, another 15 healthy children had been recruited as the control group. The ethics committee of Hebei Medical University's Second Hospital gave their approval to this study (2021-R258). The informed consent form was signed by all of the participants.

Inclusion Criteria

The HSP Inclusion Criteria

The diagnostic criteria of the HSP meet the seventh edition of "Zhufutang Practical Pediatrics", and the diagnosis can be made if the following 2 or more are met: 1) palpable purpura; 2) age of onset <20 years old; 3) acute abdominal pain; 4) tissue sections show neutrophil infiltration around venules and arterioles.

The HSPN Inclusion Criteria

Based on the Guidelines for Purpura Nephritis (9), the diagnostic criteria for hematuria and proteinuria are as follows: 1. Hematuria: gross hematuria or hematuria red blood cell ≥3/high power field (HP) 3 times within 1 week. 2. Proteinuria: those who meet any of the following: (1) three routine urine tests within 1 week qualitatively show positive urine protein; (2) 24-hour urine protein quantitative> 150 mg or urine protein/creatinine (mg/mg)> 0. 2; (3) the urine microalbumin was higher than in the normal 3 times within a week.

Exclusion Criteria

Those who have any of the following are excluded: ① There is a history of the HSP or the HSPN before admission, that is, patients who are not treated for the first

time; ② Children with acute or chronic renal dysfunction, such as kidney tumors, kidney or vascular malformations, kidney stones or abnormal renal function caused by renal tissue trauma; ③ The child has primary or other secondary kidney diseases such as nephrotic syndrome, chronic glomerulonephritis, Ig A nephropathy, thin basement membrane disease, hepatitis B virus-related nephritis, so on and so forth; ④ Children with other immune system diseases, such as Kawasaki disease, systemic lupus erythematosus, juvenile idiopathic arthritis, rheumatic diseases, as well as others.; ⑤ Those who have recently taken drugs with kidney toxic side-effects; ⑥ Those who have been treated with glucocorticoids or other immunosuppressive agents before the consultation; ⑦ Children with dysfunction of important organs such as heart, liver, and lung, and other serious systemic diseases.

Experimental Method

Specimen Collection

Peripheral venous blood was collected on an empty stomach in the early morning within 24 hours after admission in both the HSP and the HSPN groups, and blood was collected in the healthy children in the control group during the physical check-up. 3 ml peripheral venous blood was collected by blood routine anticoagulant test tube for the detection of peripheral blood lymphocyte subsets; 2 ml peripheral venous blood was collected with ordinary test tube for the detection of immunoglobulin IgA, IgM IgG, complement C3, and C4.

Detection Method

Flow cytometry detection steps

① Take 3 ml of peripheral venous blood on an empty stomach and apply EDTA tube for anticoagulation;

② Take 4 special flow-type test tubes, labeled A, B, C, D respectively, add 5ul of CD3-PC5, 10ul of CD4-FITC, and CD8-PE to A and B test tubes with a pipette, add 5ul of CD3-PC5, 10ul of CD16CD56-PE to C test tube, and add 5ul of CD3-PC5 and 10ul of CD19-FITC to D test tube;

③ Add 50ul of anticoagulated peripheral blood to each tube, shake and mix thoroughly with a mixer, and incubate in dark for 30 minutes at room temperature;

④ Add 50ul of hemolysin to each tube to lyse red blood cells, shake and mix thoroughly, and incubate in dark for 20 minutes at room temperature;

⑤ Add 500ul of pure water to each tube, shake and mix thoroughly, and incubate in dark for 15 minutes at room temperature;

⑥ Add 3ml of PBS to each tube for washing, and centrifuge in a centrifuge at 1500 rpm for 5 minutes, discard the supernatant, save the cell pellet, add 0.5 ml of PBS to each tube, shake and mix thoroughly;

⑦ After confirming the negative fluorescence range with isotype control, employ the FACS Caliber flow cytometer (American BD Company) to detect CD3+, CD4+, CD8+, CD19+, and NK cells.

Immunoglobulin, and complement detection procedures

2ml peripheral venous blood was collected from all children on an empty stomach in the morning. The serum was separated and obtained by centrifugation at 2500-3000 revolutions per minute for 5-10 min. With IMAGE 800 automatic immune analyzer, the immunoturbidimetric method was employed to detect the relevant immune indicators in the serum, including the levels of immunoglobulin IgG, IgA, IgM, and complement C3, C4, and the data obtained were then compared and analyzed.

Statistical Methods

The SPSS 21.0 was utilized in this study. The mean±standard deviation was employed to test conformity to normality, and the median and quartile were used for the test of non-conformity to normality. The normal distribution test was performed on the original data, and the differences of each observational index among the three

groups were statistically tested by a one-way analysis of variance. LSD test was made use of to compare the difference between every two groups. Had it not met the test of homogeneity of variance, then the SNK test was used. The Chi-square test was employed for discontinuous data among the groups. P<0.05 is statistically significant.

RESULTS

General Data Analysis

A total of 104 children had been recruited, 56 were males and 48 were females; all of them varied from 3-14 years of age. The average age in the HSPN group was 9±0.5 years old, the average age in the NHSPN group was 8.2±0.3 years old, the average age in the normal control group was 9.7±0.6 years old. There was no statistical difference in gender among the three groups. (Table 1 for details)

Humoral Immunity Results

The level of IgM in the control group, allergic Purpura non-nephritis group, and the nephritis group were: 1.95±0.16g/L, 1.21±0.42g/L, 1.04±1.03g/L, and the difference among the three groups was statistically significant (P<0.01).

The level of IgA in the control group, the non-nephritis group, and the nephritis group were 1.1±0.34g/l, 2.13±0.79g/l, and 2.36±1.04g/l respectively. The difference among the three groups was statistically significant (P<0.01).

The level of IgG in the control group, the non-nephritis group, and the nephritis group were: 7.18±1.3g/L, 11.19±2.78g/L, 8.93±2.04g/L, respectively. The difference among the three groups was statistically significant (P<0.01).

The level of complement C3 in the control group, the non-nephritis group, and the nephritis group were 1.34±0.15g/L, 1.07±0.23g/L, 0.91±0.24g/L, respectively. The difference among the three groups was statistically significant (P<0.01).

The level of complement C4 in the control group, the non-nephritis group, and the nephritis group were: 0.30±0.04g/L, 0.25±0.08g/L, 0.19±0.05g/L, respectively. The difference among the three groups was statistically significant (P<0.01). The details had been listed in Table 2 and Figure 1.

Cellular Immune Results

The results were shown in Table 3 and Figure 2.

The level of CD3+ in the control group, the non-nephritis group, and the nephritis

Table 1. Age and sex comparison of normal control group, purpura nephritis group and non-nephritis group

Group	Cases	Sex		Age (year)
		Male	Female	
Normal control group	15	8	7	9.7±0.6
Purpura nephritis group	36	19	17	9.0±0.5
Non nephritis group	68	36	32	8.2±0.3

Table 2. Comparison of humoral immunity in normal control group, Henoch-Schonlein purpura nephritis group and non-nephritis group

Group	IgM(g/L)	IgA(g/L)	IgG(g/L)	C3(g/L)	C4(g/L)
Control (15 Cases)	1.95±0.16	1.1±0.34	7.18±1.3	1.34±0.15	0.30±0.04
HSPN (36 Cases)	1.0±1.03*	2.3±1.04*	8.9±2.04*◊	0.91±0.24*◊	0.19±0.05*◊
NHSPN (68 Cases)	1.2±0.42*	2.1±0.79*	11.±2.78*	1.07±0.23*	0.25±0.08*

Compared with the control group *P<0.05; Compared with the non-nephritis group ◊P<0.05

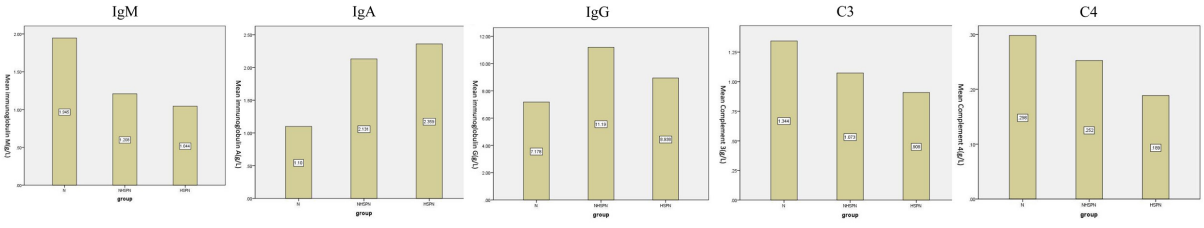

Figure 1. Comparison of IgM levels in three groups F=23.31, P<0.01; Comparison of IgA levels in three groups F=23.31, P<0.01; Comparison of IgG levels in three groups F=27.41, P<0.01; Comparison of C3 levels in three groups F=20.20, P<0.01; Comparison of C4 levels in three groups F=19.98, P<0.01.

Table 3. Comparison of cellular immunity in normal control group, purpura nephritis group and non-nephritis group

Group	CD3%	CD4%	CD8%	CD4/CD8	CD19%	NK%
Control (15 Cases)	71.33±4.18	36.86±4.34	31.53±2.92	1.18±0.05	13.79±2.38	17.92±6.66
HSPN (36 Cases)	66.74±7.23*◊	33.30±6.41*◊	28.43±5.60*◊	1.25±0.06	23.10±1.44*◊	9.29±4.57*◊
NHSPN (68 Cases)	62.02±3.94*	29.51±3.24*	25.27±2.68*	1.18±0.02	26.69±3.53*	13.68±6.28*

Compared with the control group *P<0.05; Compared with the non-nephritis group ◊P<0.05

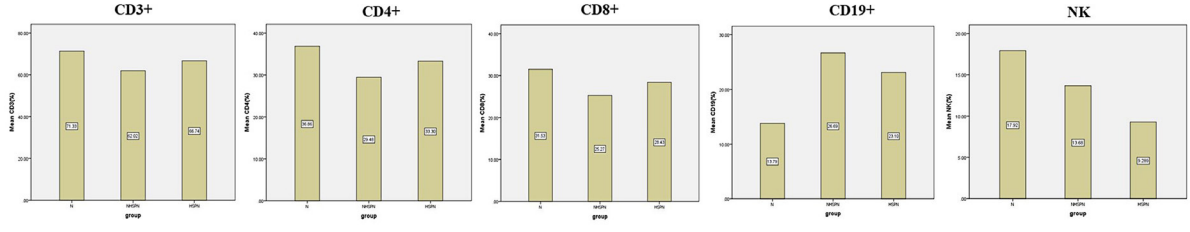

Figure 2. Comparison of CD3+ levels in three groups F=24.12, P<0.01; Comparison of CD4+ levels in three groups F=22.4, P<0.01; Comparison of CD8+ levels in three groups F=22.45, P<0.01; Comparison of CD19+ levels in three groups F=28.76, P<0.01; Comparison of CD19+ levels in three groups F=11.97, P<0.01.

group were 71.33±4.18%, 62.02±3.94%, and 66.74±7.23%, respectively. The difference among the three groups was statistically significant (P<0.01).

The level of CD4+ in the control group, the non-nephritis group, and the nephritis group were: 36.87±4.34%, 29.51±3.24%, and 33.30±6.41%, respectively. The difference among the three groups was statistically significant (P<0.01).

The level of CD8+ in the control group, the non-nephritis group, and the nephritis group were: 31.53±2.92%, 28.43±5.60%, and 25.27±2.68%, respectively. The difference among the three groups was statistically significant (P<0.01).

The CD4+/CD8+ in the control group, the non-nephritis group, and the nephritis group were: 1.18±0.05, 1.18±0.02, 1.25±0.06, respectively. The difference among the three groups was not statistically significant (P>0.05).

The level of CD19+ in the control group, the non-nephritis group, and the nephritis group were: 13.79±2.38%, 26.69±3.53%, and 23.10±1.44%, respectively. The difference among the three groups was statistically significant (P<0.01).

The level of NK cells in the control group, the non-nephritis group, and the nephritis group were: 17.92±6.66%, 13.68±6.28%, 9.29±4.57%, respectively. The difference among the three groups was statistically significant (P<0.01).

DISCUSSION

Henoch-Schoenlein Purpura might take place throughout the year. But the incidence in cold seasons such as autumn and winter increases significantly, while the incidence is lower during summer, and there is no significant difference between genders (10, 11). The upper respiratory tract infection may be the main factor leading to the onset (6). Among them, the upper respiratory tract infection caused by β-hemolytic streptococcus (GABS) was essential for the HSPN (12). Streptococcal and complement deposits were closely related to the HSPN (13, 14).

IgA is the first line of defense against the infection. The peripheral blood IgA level of children with Henoch-Schonlein Purpura was higher than in the healthy children, and the nephritis group was higher than the non-nephritis group (15, 16), and the incidence of the nephritis in children with Henoch-Schonlein Purpura had nothing to do with IgA levels (17). This study showed that IgA levels of the HSP were higher than in the healthy children. However, no difference was observed in IgA levels between the nephritis group and the non-nephritis group. It may be that the deposition of the immune complex is not organ-specific, so IgA is not different in each type of the HSP. At present, the mechanism of IgM in Henoch-Schonlein Purpura and Purpura nephritis is still not evident, and further research is needed. This study showed that the IgM levels of HSP were lower than in the healthy children. IgG is the main immunoglobulin for the body to resist the invasion of pathogenic bacteria. In this study, the IgG levels of the HSP were higher than in the healthy children; the IgG level in the nephritis group was lower than in the non-nephritis group. IgA deposition, IgA+IgG deposition, GA+IgM deposition, IgA+IgM+IgG deposition were observed in the HSPN children (18, 19) which shows that IgG is involved in the formation of the immune complexes.

The complement system is mainly via the classical activation pathway, alternative activation pathway, and lectin activation pathway (20-23) to mediate cellular immunity. The disorder of the complement system will lead to the disorder of cellular immune response. Previous studies have shown that the levels of C3, and C4 may decrease in some children (24, 25). This study showed that the C3, and C4 levels of the HSP were lower than in the healthy children, and the C3, and C4 levels of the nephritis group were lower than in the non-nephritis group. The decrease in complement may be caused by the large consumption of the activated MBL pathway and cannot be compensated by liver synthesis.

Streptococcus infection is closely related to the onset of HSP because it can cause acute inflammation, leading to the synthesis of acute-phase proteins by the liver, thereby starting the lectin activation pathway, the immune complexes cannot be cleared in time, resulting in the deposition of the immune complexes, aggravating inflammation and causing tissue damage (26, 27). The reduction of C3 and C4 is closely related to (28). Therefore, the HSP children with hypocomplementemia should be followed up for a long time.

There are CD4+ molecules on the surface of Th, and CD8+ molecules on the surface of Ts and Tc (29, 30). CD4+ T cells were important for regulating adaptive immunity. The up-regulation of OX40 and the increase of SOX40L are closely related to the HSP and the HSPN disease activities (31, 32). This study showed that the CD3+, CD4+, and CD8+ levels in the nephritis group were higher than in the non-nephritis group. The number of CD3+, CD4+, and CD8+ cells in children with the HSP and the HSPN decreased, indicating that the total number of T cells in children with the HSP and the HSPN decreased, and the cellular immune function was low, which further led to humoral immune disorders and induced diseases; while in the nephritis group, CD3+, CD4+ and CD8+ were higher than in those in the non-nephritis group, suggesting

that there may be a relative increase in T lymphocytes in children with the HSPN, leading to the activation of B cells, the increase in the number, and the production of large amounts of immunoglobulins, thereby forming and circulating the immune complexes and depositing in the kidneys, causing local immune inflammation in the glomeruli (33). It can be seen that cellular immune response occurred in the kidney tissue of patients with glomerulonephritis, and T lymphocytes participated in the occurrence and development of kidney injury (34, 35).

CD19+ is often made use of as a specific marker for B cells. Our study found that the number of B cells increased significantly in the HSP. Compared to the non-nephritis group, the percentage of B cells in the nephritis group significantly decreased. Therefore, we can conclude that B cells have a certain role to play in kidney injury.

NK cells have anti-infection and the immune regulatory functions. The reduction of CD4+ cells is mainly caused by the reduction of Th1 cells (36), which reduces the secretion of IL-2 and also reduces the number of NK cells, and the immune network formed thereby interacts and leads to the occurrence of diseases. In this study, the percentage of NK cells in the nephritis group was further reduced as compared to the non-nephritis group. This indicates that NK cells p was related to the HSP and kidney damage.

This study suggests that in the pathogenesis of the HSP and Henoch-Schonlein Purpura nephritis, there are disorders of body fluid, cellular immunity, and complement system functions, influencing each other, which coupled, lead to the occurrence of diseases. And by understanding the changes in humoral immunity and cellular immunity during the onset of children, we can further guide targeted treatment.

There have also been limitations in this study. The amount of specimens is small, the classification is not detailed enough, and the long-term follow-up observation of discharged children has not been carried out. This study only conducted a preliminary exploration of some indicators of humoral immunity and cellular immunity in peripheral serum. The change of different types of the HSP in Henoch-Schonlein Purpura nephritis still needs further research by expanding the sample size.

CONCLUSION

Immune dysfunction in children with the HSPN is specifically manifested as low cellular immune function, which leads to increased secretion of inflammatory mediators, activating B cells, and further increasing the secretion of immunoglobulins, leading to the occurrence of small vasculitis. Among them, the decrease of the level of IgM may suggest IgM immune deficiency; the significant decrease of C3, C4 levels indicate the decrease of complement system function.

ACKNOWLEDGMENTS

None

FUNDING SOURCES

Not applicable

STATEMENT OF ETHICS

Following the declaration of Helsinki, this research was carried out. The Ethics Committee of Hebei Medical University's Second Hospital gave their approval to this study (NO.: 2021-R258). All participants signed a written informed consent form.

AUTHOR'S CONTRIBUTIONS

Su QX has made substantial contributions to the conception and design, Jiang L.J. **Chai** J

and Dou ZY acquisition of data, analysis, and interpretation of data; Rong ZH and Zhao X have been involved in drafting the manuscript and revising it critically for important intellectual content; Yub, Wang YX, and Wang **X** have given their final clearance for the published version.

Conflicts of Interest: None declared.

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