Journal of Clinical and Molecular Medicine

Research Article ISSN: 2516-5593

Hypergammaglobulinemia in 2259 children with Henoch–Schönlein Purpura

Qiang Lin, Yunyan Shen, Hanyun Tang, Yun Zhu, Qinying Xu, Yanhong Li and Xiaozhong Li*

Department of Nephrology and Immunology, Children's Hospital of Soochow University, No. 303 Jingde Road, Gusu District, Suzhou 215003, China

Abstract

Background: Hypergammaglobulinemia is rarely reported in children with Henoch–Schönlein purpura (HSP), its impact on the prognosis of HSP is not clear. The aim of our study was to analyze the differences between Henoch–Schönlein purpura patients with hypergammaglobulinemia and those without hypergammaglobulinemia.

Methods: HSP patients who were hospitalized in the Children's Hospital of Soochow University between January 2014 and November 2017 were studied. Patients with serum IgG levels ≥20g/L were the case group. An equal number of HSP patients with IgG levels <20g/L were selected as the control group using random number method.

Results: 2259 HSP children were hospitalized during the period, 49 children were included in the case group. In the case group, C3 and C4 levels decreased in 18 patients, C4 was low in 12 and 19 patients had normal complement levels. Of 50 HSP patients selected as the control group, C4 was low in 2 patients, C3 was within the normal range in the entire control group. Patients in case group had higher levels of C-reactive protein, Leucocyte counts, IgA and positive titers of antistreptolysin-O ($P<0.001$), but lower levels of complement component ($P<0.001$). There were no statistical differences in age, sex, incidence of renal injury and IgM levels in the two groups. Children with renal injury presented with transient proteinuria or microscopic hematuria in both groups, and all of them recovered in 3-4 weeks. The follow-up time was 2.95±1.04 years. No sequela was found.

Conclusions: Hypergammaglobulinemia in HSP children may be related to streptococcal infection and may be associated with hypocomplementemia. This phenomenon does not affect the prognosis.

Abbreviations: HSP: Henoch–Schönlein purpura; SPSS: Statistical Program for Social Sciences; ASO: Antistreptolysin-O; ANA: Antinuclear antibody; ICs: Immune complexes; SLE: Systemic Lupus Erythematosus; URI: Upper respiratory infection.

Background

Henoch-Schönlein purpura (HSP) is predominantly a childhood vasculitic disease, mainly manifested as skin purpura, joint pain, abdominal pain and nephritis, the pathogenesis is not clear. Existing research shows that the deposition of immune complexes in the vascular wall may be one of the mechanisms. In children with HSP, the activation of B cells and the secretion of immunoglobulin increased, and the increase of IgA is most significant [1]. But hypergammaglobulinemia in HSP is rarely reported. Its impact on the prognosis of HSP is not clear.

Thus, the aim of our study was to analyze the clinical features of HSP with hypergammaglobulinemia.

Patients and methods

Patients with HSP who were hospitalized in the Children's Hospital of Soochow University between January 2014 and November 2017 were studied. We checked the laboratory results of these patients in the central laboratory database of our hospital, patients with serum IgG levels ≥20 g/L were identified. This cutoff is based on previous literature [2]. Patients with serum IgG levels <20 g/L were numbered according to the order of hospitalization time, and an equal number of patients were selected as the control group using random number method.

A single investigator abstracted relevant information for each patient from the electronic medical record. Upper Respiratory tract infection (URI) is considered to be one of the inducing factors of HSP, so patients developed URIs within 3 weeks before the onset of HSP were recorded. We analysed the laboratory data of the day on which the serum IgG result was obtained. These values included leucocyte counts, C-reactive protein (CRP), serum IgA, IgM, Antistreptolysin-O (ASO), and complement levels.

HSP was diagnosed according to the European League Against Rheumatism criteria [3]. Renal involvement was defined as gross or microscopic hematuria (>5 red blood cells per high-power microscopic field in a centrifuged specimen), or proteinuria (protein >0.3 g/24 h or a urine albumin/creatinine ratio >30 mg/mmol on a spot-check morning sample) [3].

Statistical analysis was performed using the Statistical Program for Social Sciences (SPSS) software 18.0 for Windows (SPSS, Chicago, IL, USA). Numerical variables are given as the mean ± standard deviations. Student's t-test was used to compare normally distributed

Correspondence to: Xiaozhoong Li, Department of Nephrology and Immunology, Children's Hospital of Soochow University, No. 303 Jingde Road, Gusu District, Suzhou 215003, China, E-mail: xiaozhonglicn@yeah.net

Key words: *Henoch-Schönlein purpura, hypergammaglobulinemia, streptococcal infection, hypocomplementemia*

Received: September 15, 2018; **Accepted:** September 26, 2018; **Published:** September 28, 2018

laboratory variables, values not conforming to a normal distribution and homogeneity of variance were compared with the Mann–Whitney U-test. Categorical variables were assessed using the Pearson's Chi-squared ($\chi 2$) test. A two-tailed P value was used, $P<0.05$ was considered to be significant.

Results

2259 HSP children were hospitalized in the Children's Hospital of Soochow University from January 2014 to November 2017.There were 51 patients with serum IgG levels ≥20g/L. A boy was excluded because he received Intravenous Immunoglobulin for Kawasaki disease two weeks before the onset of HSP. Another girl was excluded because she had autoimmune hepatitis, which was also associated with hypergammaglobulinemia. Therefore, 49 children were included in the case group.

In the case group, C3 and C4 levels decreased in 18 patients, C4 was low in 12, and 19 patients had normal complement levels. For patients in the control group, C4 was low in 2 patients, C3 was within the normal range.

There were no statistical differences in age, sex, incidence of renal injury and IgM level in the two groups. There were lower levels of complement component and higher IgA levels in the case group. Levels of CRP and Leucocyte counts were higher in the case group (Table 1).

There was no significant difference in the incidence of renal injury between the two groups. The patients with renal injury were characterized by transient proteinuria or microscopic hematuria, and all recovered within 3-4 weeks.

In the case group, 4 patients were not tested for ASO, and all patients in the control group had ASO results. We analyzed the ASO positive rate and the titer levels in the two groups after excluding the 4 patients who didn't do the test.

The positive rate of ASO in the IgG elevated group was significantly higher than that in the control group. The ASO titer of the IgG group was 1041.53±689.51 IU/ml and compared with the118.40±172.64 IU/ml of the control group, there was also a statistical difference (Table 2).

Of the 49 patients in the case group, 14 patients didn't test autoantibodies. Of 35 patients examined for autoantibodies, 24 patients were normal, and 11 had positive results. Antinuclear antibody (ANA) was positive in a six-year-old girl with a titer of 1:1000 on the day of hospitalization, the titer dropped to 1:320 seven days later, her IgG value was 24.32 g/L, her C3 and C4 were normal. The titer of ANA was 1:100 in 6 patients and 1:320 in 1. Ro52 was positive in 2 patients, it was 1:100 and 1:320 respectively. One patient had a positive Jo-1 antibody, which was 1:100.

Table 1. Comparison of clinical features and laboratory values in the two groups

	Case group, n=49	Control group, n=50	P values
Sex	male 25, female 24	male 27, female 23	0.841
Age(years)	7.61±2.42	7.40±2.91	0.697[a]
URI	31(63.26%)	22(44.00%)	0.055
Renal injury	11(22.45%)	10(20.00%)	0.810
IgA(g/L)	3.24±1.02	2.13±0.71	<0.001[b]
IgG(g/L)	23.23±3.11	10.40±2.90	<0.001[a]
IgM(g/L)	1.49±0.65	1.30±0.59	0.149[a]
C3(g/L)	0.96±0.37	1.20±0.19	<0.001[b]
C4(g/L)	0.14±0.13	0.33±0.11	<0.001[b]
Leucocyte counts	12.93±4.02	10.88±4.37	0.009[b]
CRP	18.59±22.49	9.87±14.29	0.004[b]

Normal C3 levels are 0.79–1.52 g/L.
Normal C4 levels are 0.16–0.38 g/L
a: t-test.
b: Mann–Whitney U-test.

Table 2. Positive rate of ASO and ASO levels in the two groups

	Case group, n=45	Control group, n=50	P values
Patients with positive ASO	39 (86.67%)	10 (20.00%)	< 0.001
Levels of ASO titers (IU/ml)	1041.53±689.51	118.40±172.64	< 0.001[a]

Normal value of ASO is less than 250 IU/mL.
a: Mann–Whitney U-test.

The follow-up period lasted for 2.95±1.04 years, and no complications or other diseases were found.

Discussion

Abnormal glycosylation of IgA1 hinge area causes IgA-type autoantibodies in children with HSP. Immune complexes (ICs) are formed when abnormal glycosylated IgA combines with IgA autoantibodies (IgA-IgA-ICs) or antiglycan IgG (IgA-IgG-ICs). These IC's can injure vascular endothelial cells through a complement-dependent pathway and are likely to play a pathogenic role in HSP [1,4,5].

Lau *et al.* showed that HSP nephritis patients had elevated levels of IgG against galactose-deficient IgA1 when compared to those HSP patients without nephritis and controls [1], but hypergammaglobulinemia in HSP was identified rarely in previous study [2]. Our survey showed that the incidence of hypergammaglobulinemia in children with HSP was 2.17% (49/2259). But we did not find that hypergammaglobulinemia could increase the incidence and severity of renal injury.

The cause of hypergammaglobulinemia in HSP is not clear.

Rukako Tamai reported a 72-year-old HSP patient with hypergammaglobulinemia and hypocomplementemia. He found that IgG4 account for 25% of the IgG molecules. He believes that IgG4-related tubulointerstitial nephritis and HSP together led to renal injury in that patient [6]. IgG4-related diseases are characterized by hyperglobulinemia and hypocomplementemia [7], IgG4 related diseases should be distinguished from HSP [8].

IgG4-related tubulointerstitial nephritis are usually characterized by renal insufficiency, and the IgG4 related diseases are mainly seen in adults. Children with IgG4 related diseases are very rare [7,9].

There was no renal insufficiency in these children in our study, so we inferred that these children did not have IgG4 related disease even though we didn't analyses IgG subclass.

In our study, HSP patients with hypergammaglobulinemia had a high rate of streptococcal infection, and the complement C3 and C4 were also significantly lower than those patients in the control group. It suggests that streptococcal infection may be the cause of the increase in immunoglobulin, but the reason for the serologic response to streptococcal infections is not clarified.

Some scholars believe that HSP can overlap with cryoglobulinemia. Hemolytic streptococci can remove sialic acid from IgG, promote the formation of cryoglobulin, and the activation of the complement system, which can result in reduced serum complement [4]. The relationship between hypergammaglobulinemia and cryoglobulinemia needs to be further studied.

In the case group, 35 patients were tested for autoantibodies to rule out Systemic Lupus Erythematosus (SLE) and other kinds of autoimmune disease and 11 patients had positive results. The literature reports that autoantibodies can be detected in HSP patients [10]. Some scholars have found that SLE can be secondary to or coexisting with HSP [11]. In our study no patient developed SLE in our follow up.

Conclusions

Hypergammaglobulinemia is a rare phenomenon in HSP. Hypergammaglobulinemia may be associated with streptococcal infection and is likely to cause hypocomplementemia, but it does not affect the incidence of renal injury.

Ethics approval and consent to participate

The study was carried out in accordance with the ethical standard laid down in the Declaration of Helsinki. Informed consent was obtained from the children and their parents. The study was approved by the ethics committee of the Children's Hospital of Soochow University.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This project was supported by the National Natural Science Foundation of China (Grant Number: 81370787), Clinical Medical Science and Technology Commission of Jiangsu Province (Grant Number: SBL2014030237) and Suzhou Key Laboratory of Nephrology (Grant Number: SZS201511).

Authors' contributions

Qiang Lin and Yunyan Shen contributed equally to this work and share first authorship.

Acknowledgements

Not applicable

References

1. Lau KK, Suzuki H, Novak J, Wyatt RJ (2010) Pathogenesis of Henoch-Schönlein purpura nephritis. *Pediatr Nephrol* 25: 19-26. [Crossref]

2. Lo MS, Zurakowski D, Son MB, Sundel RP (2013) Hypergammaglobulinemia in the pediatric population as a marker for underlying autoimmune disease: a retrospective cohort study. *Pediatr Rheumatol Online J* 11: 42. [Crossref]

3. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, et al. (2010) EULAR/PRINTO/PRES criteria for Henoch–Schönlein purpura, childhood polyarteritis nodosa, childhood Wegener granulomatosis and childhood Takayasu arteritis: Ankara 2008 Part II: final classification criteria. *Ann Rheum Dis* 69:798–806. [Crossref]

4. Lin Q, Min Y, Li Y, Zhu Y, Song X, et al. (2012) Henoch–Schönlein purpura with hypocomplementemia. *Pediatr Nephrol* 27: 801–806. [Crossref]

5. Yang YH, Yu HH, Chiang BL (2014) The diagnosis and classification of Henoch–Schönlein purpura:an updated review. *Autoimmun Rev* 13: 355–358. [Crossref]

6. Tamai R1, Hasegawa Y, Hisano S, Miyake K, Nakashima H, et al. (2011) A case of IgG4-related tubulointerstitial nephritis concurrent with Henoch-Schönlein purpura nephritis. *Allergy Asthma Clin Immunol* 7: 5. [Crossref]

7. Fang Y, Hou J, Cai F, Ding XQ, Liu H (2012) IgG4-associated tubulointerstitial nephritis: two case reports and a literature review. *Intern Med* 51: 2385-2391. [Crossref]

8. Tokura Y, Yagi H, Yanaguchi H, Majima Y, Kasuya A, et al. (2014) IgG4-related skin disease. *Br J Dermatol* 171: 959-967. [Crossref]

9. Faiz K, Jan L, Wichor B, Lauren W, Rob V, et al. (2016) IgG4-related disease: a systematic review of this unrecognized disease in paediatrics. *Pediatr Rheumatol Online J* 14: 18. [Crossref]

10. Calvo-Río V, Loricera J, Mata C, Martín L, Ortiz-Sanjuán F, et al. (2014) Henoch-Schönlein purpura in northern Spain clinical spectrum of the disease in 417 patients from a single center. *Medicine (Baltimore)* 93: 106-113. [Crossref]

11. Hu P, Huang BY, Zhang DD, Jiang GM, Liu SY, et al. (2017) Henoch-Schönlein purpura in a pediatric patient with lupus. *Arch Med Sci* 13: 689–690. [Crossref]