Predisposing factors of childhood Henoch-Schönlein purpura in Anhui province, China

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ABSTRACT

Henoch-Schönlein purpura (HSP) is a common autoimmune vasculitis in childhood. The detailed pathogenesis of HSP is still unclear, whereas several types of predisposing factors have been proved to be the initial step. The objectives of present study were to analyze the distribution of predisposing factors, association of the predisposing factors with clinical manifestations and HSP relapse/recurrence. 1200 children with HSP were recruited between January 2015 and December 2017. We reviewed their laboratory tests and medical histories associated with HSP onset. The annual incidence of HSP was 8.13–9.17 per 100 000 in Anhui province. HSP occurred more commonly in spring and winter than in summer with an obvious west-to-east gradient. Cutaneous purpura was the most prevalent manifestation (100%), followed by arthritis/arthralgias (43.67%), abdominal pain (40.17%) and renal involvement (18.17%). On admission, series of potential infections were identified in 611 patients (50.92%). The histories of allergy, injury, surgery, vaccination and tick bite were declared by 231 patients (19.25%), 15 patients (1.25%), 12 patients (1.00%), 4 patients (0.33%) and 3 patients (0.25%), respectively. However, predisposing factors could not be identified in 521 children with HSP (43.42%) yet. 123 cases (10.25%) relapsed or recurred more than one time; the mean number was 2.92, and the mean interval was 11.4 weeks. The infection is the most frequent predisposing factor regardless of clinical phenotypes and relapse/recurrence, whereas the clinical manifestations exhibit an obvious heterogenicity according to different predisposing factors.

Significance of this study

What is already known about this subject?

- Although Henoch-Schönlein purpura (HSP) is usually considered as a common self-limiting vasculitis in childhood, sometimes it can also be life-threatening if systemic inflammation persists or multiple internal organs are involved.
- Currently, the detailed pathogenesis of HSP is still unclear, whereas several types of predisposing factors have been proved to be the initial step of HSP onset.
- The multiple environmental factors and genetic backgrounds in China account for different epidemiological features of HSP; up to now, no published data have been documented from central China.

What are the new findings?

- HSP occurs more commonly in spring and winter than in summer; its morbidity has an obvious west-to-east gradient in Anhui province, undergoing a 10-fold increase in the western as compared with the eastern.
- The infection is the most frequent predisposing factor of HSP regardless of clinical phenotypes and relapse/recurrence, whereas the clinical manifestations exhibit an obvious heterogenicity according to different predisposing factors.

How might these results change the focus of research or clinical practice?

- Streptococcal infection accounts, in part, for the dramatic seasonal variation of HSP onset in Anhui province, China.
- The identification of predisposing factors may be beneficial in the prevention of HSP progression and relapse/recurrence.

INTRODUCTION

Henoch-Schönlein purpura (HSP) is a common autoimmune vasculitis affecting children aged <16 years and exhibits a series of characteristic symptoms, including non-thrombocytopenic purpura, arthritis/arthralgia, abdominal pain, gastrointestinal bleeding and glomerulonephritis.[1] Although HSP is usually considered as a self-limiting disease, sometimes it can also be life-threatening if systemic inflammation persists or multiple internal organs are involved. An epidemiological survey in Taiwan, China from 1999 to 2002 demonstrated that a total of 2759 children with HSP were recruited with an annual incidence of 12.9 per 100 000 children.[2] HSP accounts for 58.0% in pediatric primary vasculitis and the peak age occurs between 4 and 9 years.[3] Renal damage is one of the substantial factors for HSP prognosis. Based on the data from 13 studies encompassing 2398 children with HSP, a meta-analysis by Chan *et al*[4] indicated that 40.6% of them had renal involvement, and moreover male gender, aged >10

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years, severe gastrointestinal symptoms, arthritis/arthralgia, persistent/relapse purpura, leukocytosis, thrombocytosis, elevated antistreptolysin O (ASO), decreased complement component 3 (C3) and proteinuria were predictive of end-stage renal disease. In contrast, an epidemiological analysis of 13 519 renal biopsies from a single unit in China showed that 20.3% prevalent etiology of secondary glomerulonephritis may be derived from the juvenile HSP.[5] Currently, the detailed pathogenesis of HSP is still unclear, whereas several types of predisposing factors have been proved to be the initial step. Furthermore, emerging lines of evidence suggest that genetic factors are also associated with HSP susceptibility. To date, series of genome-wide association studies have showed that the genetic variations in Mediterranean fever and ACE may confer susceptibility to HSP in Chinese Han population, in comparison with the other 37 candidate genes.[6]

Numerous epidemiological studies have documented several types of predisposing factors participating in HSP onset, such as infective agents, foods, drugs, vaccinations, insect bites and so on. Trapani *et al*[7] retrospected the discharge coding data from Meyer Children's Hospital, Italy since 1998–2002, and found that the most common trigger of HSP was respiratory tract infection (42%), followed by gastrointestinal infection (5%), other infection (4%), vaccination or tick bite (2%), whereas 47% cases still could not be identified clearly. In China, Liu *et al*[8] analyzed a clinical data of 325 hospitalized children with HSP since 2012–2014 in Lanzhou, and revealed that respiratory tract infection was the major factor to trigger HSP (53.5%), besides gastrointestinal infection (2.2%), cellulitis (0.9%), urinary tract infection (0.6%), food (3.7%), vaccination (1.2%) and injury (0.3%). In another Chinese retrospective study included 120 cases between 2007 and 2010 from Jinan, the most prevalent incidence of HSP triggers were respiratory tract infection (57.5%), gastrointestinal infection (3.3%), parasite infection (3.3%), food allergy (26.7%) and vaccination/tick bite (4.1%).[9] Therefore, the distribution of HSP predisposing factors varies significantly among different populations and regions.

China lies in Eastern Asia and on the western shores of the Pacific Ocean with a total land area of about 9.6 million km^2. The climate appears diverse across the Mainland China. The majority part of Chinese territory is situated in the Temperate Zone, its southern part in the Tropical or Subtropical Zone, and its northern part near the Frigid Zone.[10] As a large united multinational state, China is composed of 56 ethnic groups. In these circumstances, the multiple environmental factors and genetic backgrounds may account for different epidemiological features in China. To the best of our knowledge, only two corresponding investigations on HSP epidemiology are available from western and eastern China, respectively,[8 9] no published data have been documented from central China up to now. Due to the inadequacy of the hierarchical medical system in China, too many immigrant patients with HSP flood into the tertiary hospitals in Chinese developed regions, and most of them are not the initial cases. Anhui province is located in central China, and encompasses 139 600 km^2 and a population of 69.12 million. Because HSP is also very prevalent in Anhui and the local level of economic development is between western and eastern China, it is reasonable for us to consider the epidemiological features in Anhui may be different from the other regions in China. On this basis, the present study will be warranted to cover this gap.

METHODS

Patient selection

A total of 1200 children with HSP, younger than 16 years, were recruited in the present study between January 2015 and December 2017. Approval for this research was acquired from the Medical Ethic Committee of the First Affiliated Hospital of Anhui Medical University and obtained consent from parents. The diagnosis was based on European League against Rheumatism criteria for HSP classification.[11] All cases developed skin purpura, simultaneously accompanied

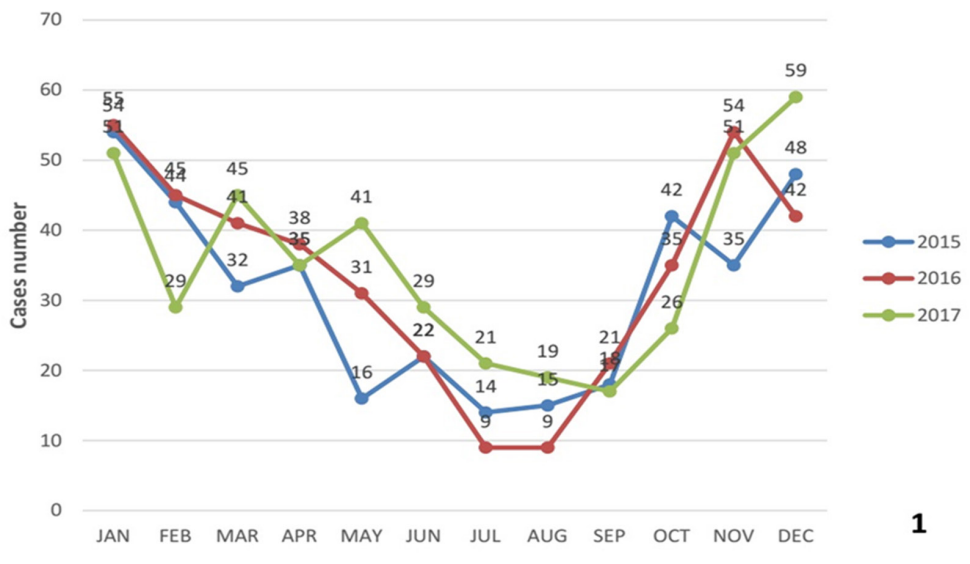

Figure 1 Monthly distribution of 1200 children with Henoch-Schönlein purpura from 2015 to 2017.

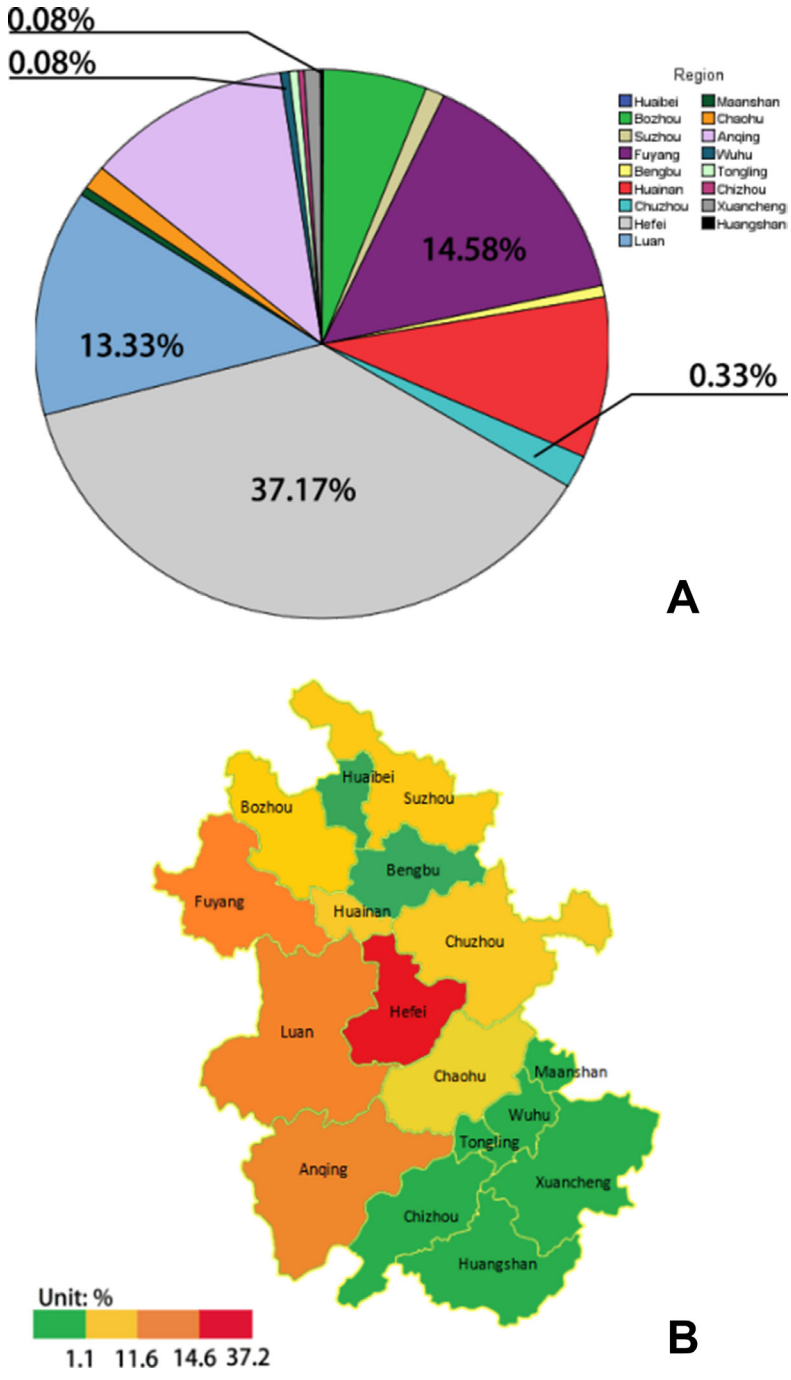

Figure 2 Region distribution of 1200 children with Henoch-Schönlein purpura from 2015 to 2017.

with at least one of the four following symptoms: (1) abdominal pain: diffuse abdominal colicky pain with acute onset assessed by history and physical examination, also including intussusception and gastrointestinal bleeding. (2) Histopathology: typically leukocytoclastic vasculitis with predominant IgA deposit or proliferative glomerulonephritis with predominant IgA deposit. (3) Arthritis or arthralgias: arthritis of acute onset defined as joint swelling or joint pain with limitation on motion. Arthralgia of acute onset defined as joint pain without joint swelling or limitation on motion. (4) Renal involvement: proteinuria: >0.3 g/24 hours or >30 mmol/mg of urine albumin/creatinine ratio on a spot morning sample. Hematuria or red blood cell casts: >5 red blood cells/high power field or red blood cells casts in the urinary sediment or ≥2+ on dipstick. The exclusion criteria were: (1) patients with incomplete information; (2) patients unable to comply with the treatment and (3) patients with severe heart, liver, lung, kidney or other organ system diseases.

Data collection

Patients underwent laboratory tests such as blood cell counts, urine tests, fecal occult blood, C reaction protein,

Table 1 Clinical manifestations and predisposing factors in Henoch-Schönlein purpura on admission

Clinical manifestations	Number of cases (%)	Predisposing factors	Number of cases (%)
Purpura	1200 (100)	Infection	611 (50.92)
Arthritis/arthralgia	524 (43.67)	Respiratory tract infection	569 (47.42)
Upper extremities	70 (5.83)	Gastrointestinal infection	75 (6.25)
Lower extremities	424 (35.33)	Urinary tract infection	16 (1.33)
Both upper and lower extremities	30 (2.50)	Streptococcal infection	205 (17.08%)
Abdominal pain	482 (40.17)	*Helicobacter pylori* infection	71 (5.92)
Isolated abdominal pain	405 (33.75)	*Mycoplasma* infection	58 (4.83)
Gastrointestinal bleeding not associated with the following situations	68 (5.67)	*Tubercle bacillus* infection	1 (0.08)
Intussusception	3 (0.25)	*Toxoplasma gondii* infection	1 (0.08)
Appendicitis	2 (0.17)	Allergy	231 (19.25)
Ileus	2 (0.17)	Food allergy	196 (16.33)
Pancreatitis	2 (0.17)	Drug allergy	21 (1.75)
Renal involvement	218 (18.17)	House dust mite allergy	10 (0.83)
Proteinuria	69 (5.75)	Grass pollen allergy	4 (0.33)
Hamaturia	55 (4.58)	Injury	15 (1.25)
Hematuria plus albuminuria	94 (7.83)	Surgery	12 (1.00)
		Vaccination	4 (0.33)
		Tick bite	3 (0.25)
		Unknown	521 (43.42)

erythrocyte sedimentation rate, ASO, *Toxoplasma gondii*, others, rubella virus, cytomegalovirus, herpes virus, Epstein-Barr virus, *Helicobacter pylori* (HP), *Mycoplasma* (MP) antibodies, tubercle bacillus (TB) antibody, respiratory pathogens (*Legionella pneumophila*, *Chlamydia pneumoniae*, adenovirus, respiratory syncytial virus, influenza A virus, influenza B virus, *Rickettsia*, parainfluenza virus), aspartate aminotransferase, alanine aminotransferase, creatine kinase (CK), CK-MB, creatinine, blood urea nitrogen, C3, C4 and IgA. Patients' histories associated with HSP onset (foods, drugs, vaccinations, insect bites) were obtained by interviews and questionnaires.

Statistical analysis

Normally distributed continuous data were expressed as mean±SD. Comparisons of the frequencies between groups were analyzed using χ^2 tests. Comparison of mean values among groups was carried out using one-way analysis of variance, and post hoc analysis was calculated using the Student-Newman-Keuls test. All p values were two-sided and $p<0.05$ were considered significant. Statistical analyses were performed using the statistical package for social studies SPSS V.16.0.

RESULTS

Demographic features

A total of 1200 children suffered from HSP, younger than 16 years, including 672 (56%) boys and 528 (44%) girls between January 2015 and December 2017 (male:female=1.27:1). The average age was 9.05±2.82 years and median age was 9 years (95% CI 8.99 to 9.11). IQR for the onset age fell in the interval between 7 and 9 years. The annual incidence of HSP was 8.13–9.17 per 100 000, which was calculated according to the demographic data from Anhui Health and Family Planning Commission. The monthly distribution of children with HSP is showed in figure 1. A bimodal distribution for HSP onset occurred in every year that were January and December in 2015, January and November in 2016, January and December in 2017, respectively. On the contrary, the lowest onset of HSP appeared in July, August or September during our observational period. In the present study, all 3 years exhibited an identical seasonal pattern, and HSP occurred more commonly in spring and winter than in summer. The geographical distribution of children with HSP is presented in figure 2. The cities with the highest proportion were clustered together in the central region of Anhui province. More specifically, Hefei had the highest proportion (37.17%), followed by Fuyang (14.58%) and Luan (13.33%), whereas Huangshan and Huaibei occupied the lowest proportion at 0.08%. The morbidity of HSP showed an obvious west-to-east gradient in Anhui province, and it underwent a 10-fold increase in the western as compared with the eastern. However, no significant difference was found from south to north.

Clinical manifestations on admission

The major clinical manifestations of HSP are shown in table 1. *Purpura* consisted of the characteristic skin lesions 2–10 mm in diameter. It was concentrated on the buttocks and lower extremities, but not restricted to those areas. Since cutaneous purpura is the necessary element in the diagnosis of HSP, all patients in our study had skin lesions. *Arthritis/arthralgia*, the second most prevalent feature of HSP, occurred in 43.67% of patients and affected the knees and/or ankles most commonly (35.33%) leading to severe pain and even walking restriction. The joints of the lower extremities were involved in 5.83% of patients. *Abdominal pain* was observed in 40.17% of patients who dominantly suffered from gastrointestinal bleeding, intussusceptions, appendicitis or ileus. Gastrointestinal bleeding was usually occult (3.50%), but 2.17% of patients had grossly bloody

or melanotic stools. This study also encountered three cases (0.25%) with intussusceptions, two cases (0.17%) with appendicitis, two cases (0.17%) with ileus and two cases (0.17%) with pancreatitis. *Renal involvement* in HSP is diverse and manifested as proteinuria and/or hematuria. In the present study, 218 cases (18.17%) were involved in kidney injury; among them, 69 cases (5.75%) had proteinuria, 55 cases (4.58%) had hematuria and 94 cases (7.83%) had hematuria and proteinuria simultaneously. In addition, *other clinical manifestations* including cardiac damage (5.00%) and liver dysfunction (1.33%) were also found in the present study.

Predisposing factors on admission

The predisposing factors of HSP are shown in table 1. On admission, series potential infections were identified in 50.92% of 1200 children with HSP. According to the site of infection, 569 cases (47.42%) had a respiratory tract infection, 75 cases (6.25%) had a gastrointestinal infection and 16 cases (1.33%) had a urinary tract infection; based on the results of laboratory examination, there were 205 cases (17.08%) with streptococcal infection, 71 cases (5.92%) with HP infection, 58 cases (4.83%) with MP infection, 1 case (0.08%) with TB infection and 1 case (0.08%) with *Toxoplasma gondii* infection. The allergic histories obtained by questionnaires discovered 231 patients (19.25%) with positive declarations, including 196 cases (16.33%) with food allergy, 21 cases (1.75%) with drugs, 10 cases (0.83%) with house dust mite and 4 cases (0.33%) with grass pollen. In the present study, 15 (1.25%) and 12 (1.00%) cases suffered from injury and surgery, respectively. Moreover, four cases reported a cutaneous rash after being immunized with rabies vaccine or meningitis vaccine within 1 week, and three cases complained a recent history of tick bites. However, the predisposing factors could not be identified in 521 children with HSP (43.42%) yet.

Association of predisposing factors with clinical manifestations

The association of predisposing factors with clinical manifestations in patients with HSP is shown in figure 3. Significant variations in the predisposing factor distribution were observed among children with HSP with different clinical manifestations (x^2=19.38, p=0.02). The infection was the most prevalent predisposing factor in children with HSP regardless of clinical phenotypes, and was detected in 56.68% of cases with arthritis/arthralgia, 50.92% of cases with purpura, 49.17% of cases with abdominal pain and 49.08% of cases with renal involvement. In addition, the allergy served as the second most prevalent predisposing factor contributing to HSP onset, and was detected in 19.25% of cases with purpura, 18.26% of cases with abdominal pain, 16.41% of cases with arthritis/arthralgia and

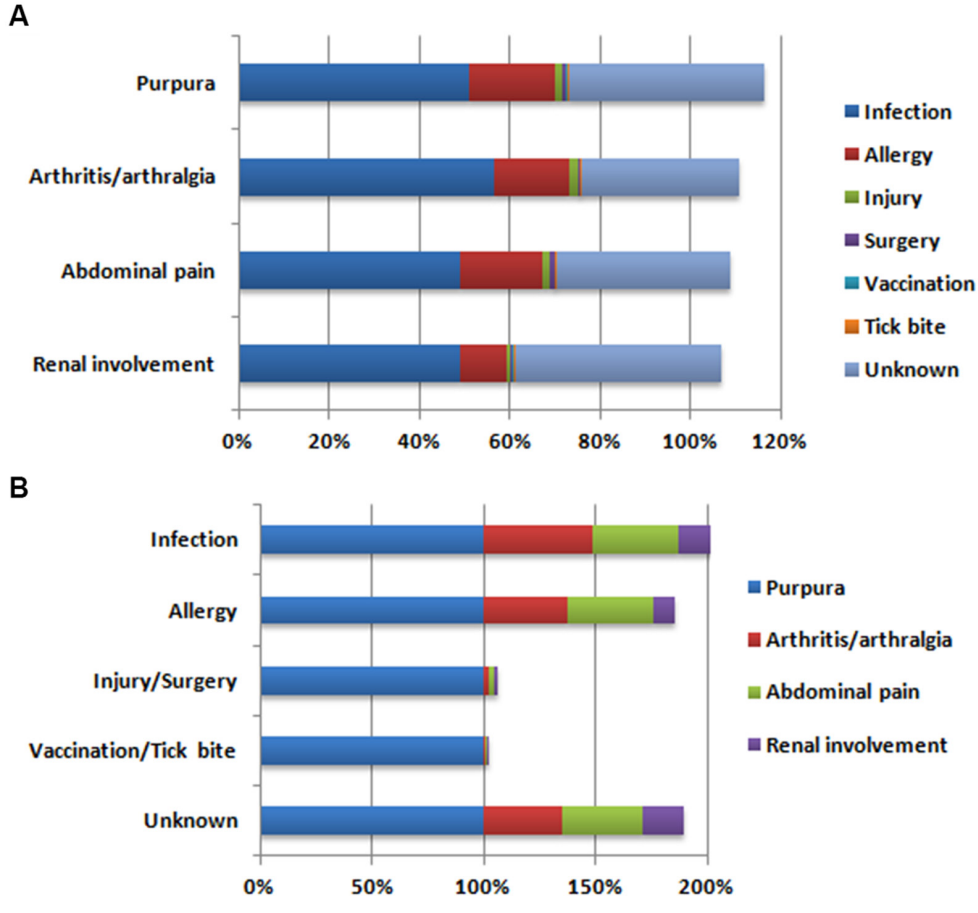

Figure 3 Association of predisposing factors with clinical manifestations.

10.09% of cases with renal involvement (figure 3A). On the other hand, the clinical manifestations exhibited an obvious heterogenicity according to different predisposing factors ($x^2=19.58$, $p=0.02$). Besides purpura, arthritis/arthralgia (48.61%) was the most common phenotype in these cases triggered by infection, as compared with abdominal pain (37.81%) and renal involvement (17.51%); abdominal pain (38.10%) and arthritis/arthralgia (37.23%) were more prevalent in cases with a clear history of allergy than those with renal involvement (9.25%). Among 218 children with HSP with renal involvement, 17.51% and 9.52% of them were associated with infection and allergy, respectively, whereas 19% of them had no clear predisposing factors (figure 3B).

Influence of predisposing factors to relapse/recurrence

Out of 1200 children with HSP, 123 (10.25%) were hospitalized more than one time from January 2015 to December 2017. Relapse/recurrence was defined when a patient previously diagnosed with HSP and asymptomatic for at least 2 weeks, presented again a new flare of cutaneous lesions or other systemic manifestations of the vasculitis.[12] The number of relapse/recurrence ranged from 2 to 10 with a mean of 2.92 during the observational period. The relapse/recurrence occurred over a time span ranged from 2 weeks to 139 weeks, with a mean of 11.4 weeks after initial resolution of symptoms. In 123 cases with relapse/recurrence, the infection was the most frequent predisposing factor (39.68%), followed by allergy (6.88%) and injury/surgery (0.53%), respectively; and moreover, 56.61% of them had no clear predisposing factors. In the other 1077 cases without relapse/recurrence, the infection was also the most frequent predisposing factor (53.02%), followed by allergy (21.56%), injury/surgery (2.57%) and vaccination/tick bite (0.69%), respectively; however, there were 40.95% of cases who had no clear predisposing factors. Significant differences in the predisposing factor distribution were observed between the above two groups. The frequencies of infection, allergy, injury/surgery and vaccination/tick bite were significant elevated in these cases without relapse/recurrence as compared with their counterparts ($x^2=36.84$, $p<0.01$).

DISCUSSION

In the present study, we recruited 1200 children with HSP within the latest 3 years. The annual incidence ranged from 8.13 to 9.17 per 100 000 based on the demographic data of Anhui province, a little lower than the previous study from Taiwan (12.9 per 100 000) 13 years ago.[2] Because the disease course of HSP is usually benign and self-limited, hospitalization is not always indicated. The hospitalization rate for HSP is estimated about 80% in our center. Therefore, if we only use the available hospital discharge data to investigate predisposing factors, 20% of patients may be ignored. In addition, the present study provides, for the first time, a reference range of HSP incidence in Mainland China. To the best of our knowledge, no information on HSP incidence has been reported in Mainland China up to date.

Cutaneous purpura is the necessary element in HSP diagnosis. Histologically, skin lesions are characterized by vessel wall necrosis, inflammatory cell infiltration and IgA deposition.[13] However, skin biopsy is neither a compulsory tool for HSP diagnosis nor a routine marker for its progression.[14] Abdominal pain severs as another common symptom in children with HSP and is mainly due to peritoneal or visceral small vessel vasculitis.[15] Furthermore, the immunosuppressive agents exert therapeutic effects by alleviating inflammatory status, but whether they also cause abdominal pain is somewhat controversial.[16] In the present study, 482 patients complained of abdominal pain, and 15.6% of gastrointestinal symptoms preceded skin lesions. Consistent with the previous report from northwestern Spain, Calviño *et al*[17] retrospected the clinical records of 78 patients with HSP in combination with abdominal pain, and found that 16.7% of gastrointestinal symptoms preceded skin lesions. Therefore, the situation of abdominal pain prior to skin lesions has often posed a diagnostic challenge to pediatricians, and endoscopy appears to have substantial diagnostic utility in those who suspected of having HSP.[18] In this study, upper endoscopy was conducted in 59 patients and showed multiple discrete coin-like petechiae and hemorrhagic erosions in the gastric antrum and lower body. As we all know, renal involvement is the most important prognostic factor for HSP, and usually exhibits transitory microscopic hematuria and/or low-grade proteinuria in the first 3 months after HSP diagnosis.[19] Pathological changes of HSP nephritis mainly contain acute episodes of glomerular inflammation with endocapillary and mesangial proliferation, whereas fibrin deposits and epithelial crescents can either heal spontaneously or lead to chronic kidney disease.[20] In the present study, 13 patients underwent renal biopsy because of persistent hematuria and/or proteinuria >6 months. According to the criteria proposed by the International Study of Kidney Disease in Children,[21] nine patients were classified as class IIIb, three patients with class IIIa and one patient with class IIb. Interestingly, other systemic manifestations including cardiac damage (5.00%) and liver dysfunction (1.33%) were also found in the present study. In 60 patients with cardiac damage, 9 patients relapsed more than two times because of persistent cutaneous purpura, hematuria or proteinuria; however, only one relapsed among 16 patients with liver dysfunction. Michas *et al*[22] reported an adolescent patient who presented with acute heart failure as a consequence of myocardial involvement in the context of HSP, and considered the pathogenesis of myocarditis might be attributed to infectious agents, systemic inflammation, drugs and autoimmune disorders, etc. To our knowledge, the studies on HSP-associated liver dysfunction were seldom reported.

The etiology of HSP is unknown, but several types of predisposing factors have been documented.[7 23] The distribution features of predisposing factors throughout the world have been presented in table 2. In the present study, 611 children with HSP suffered from series potential infections; among them, 569 cases (47.42%) had a history of respiratory tract infection and 205 cases (17.08%) had streptococcal infections; in addition, HSP onset was subject to a dramatic seasonal variation and occurred more commonly in spring and winter than in summer, coinciding with streptococcal infection. Weiss *et al*[24] conducted a retrospective cohort study including 3132 admissions for HSP observed from January 2002 to December 2008, and found a significant association between admission for HSP and streptococcal infection with prominent peaks in the fall and winter. More specifically, the present study indicated that 39 from 205 HSP cases with streptococcal infection had renal

Table 2 The predisposing factors of Henoch-Schönlein purpura throughout the world

	Anhui, China	Gansu, China[8]	Shandong, China[9]	Al-Khobar, Saudi Arabia[37]	Kuwait, Kuwait[38]	Florence, Italy[7]	Santander, Spain[23]
Number of cases	1200	325	120	78	82	150	417
Observational period	2015–2017	2012–2014	2007–2010	1996–2010	1988–2003	1998–2002	1975–2012
Predisposing factors							
Infection							
Respiratory tract infection	569 (47.42%)	174 (53.54%)	69 (57.5%)	41 (52.56%)	37 (45.12%)	63 (42%)	137 (32.85%)
Gastrointestinal infection	75 (6.25%)	7 (2.16%)	4 (3.3%)	–	–	7 (4.67%)	–
Urinary tract infection	16 (1.33%)	2 (0.62%)	–	–	–	–	–
Streptococcal infection	205 (17.08%)	–	–	–	–	–	–
Other infection	131 (10.92%)	3 (0.92%)	4 (3.3%)	2 (2.56%)	–	6 (4%)	22 (5.28%)
Allergy	231 (19.25%)	12 (3.69%)	32 (26.67%)	–	6 (7.31%)	–	77 (18.47%)
Vaccination	4 (0.33%)	4 (1.23%)	3 (2.5%)	–	8 (9.76%)	2 (1.33%)	–
Tick bite	3 (0.25%)	-	2 (1.67%)	1 (1.28%)	1 (1.22%)	1 (0.67%)	–
Injury	15 (1.25%)	1 (0.31%)	–	–	–	–	–
Surgery	12 (1.00%)	-	–	–	–	–	–
Unknown	521 (43.42%)	123 (37.85%)	4 (3.33%)	34 (43.59%)	30 (36.59%)	71 (47.33%)	–

involvement (19.02%). In a previous case-control study from Jordan, ASO positivity caused a 10-fold increase in the risk of HSP and contributed to 27% of renal involvement.[25] Nephritis-associated plasmin receptor triggered by streptococcus has been positively identified to have a diffuse and global distribution in mesangium and may play a pathogenetic role in patients with HSP nephritis.[26] Other infectious agents, such as HP and MP, have also been proved to participate in HSP onset. In the present study, the evidence of HP and MP infection was identified in 71 (5.92%) and 58 (4.83%) cases, respectively. The etiology of HP/MP-associated HSP is mainly ascribed to immune-complex-mediated injury, cytotoxic T-cell-mediated immune responses and autoimmune reactions.[27 28] Very interestingly, in the present study, we encountered an unusual case of HSP in combination with pulmonary tuberculosis in a girl aged 13 years. After treatment with isoniazid (10 mg/kg/day), rifampicin (20 mg/kg/day) and pyrazinamide (20 mg/kg/day) for 2 weeks, her cutaneous purpura disappeared, abdominal pain resolved and cough stopped. However, further studies will be warranted to probe the potential mechanisms in the future.

About five decades ago, HSP had been termed anaphylactoid purpura because HSP developed after exposure to drug, food and other allergens.[29] In the present study, the allergic histories obtained by questionnaires indicated 231 patients (19.25%) with positive declarations, including 196 cases (16.33%) with food allergy, 21 cases (1.75%) with drugs, 10 cases (0.83%) with house dust mite and 4 cases (0.33%) with grass pollen. Abnormality of the immune response, such as functional imbalance of Th2 cell subsets and a strongly polarized cytokine milieu in the peripheral blood, to environmental stimuli may contribute to either allergic or autoimmune disease.[30 31] Burton *et al*[32] explored the accelerative effects of IgE and mast cells on the accumulation of type 2 innate lymphoid cells (ILC2) at intestinal mucosal surfaces, and revealed that ILC2 cells could upregulate the expressions of IL-4/IL-13 and subsequently promoted the sensitization and effector phases of the allergic response in collaboration with mast cells. In addition, in the present study, four cases complained a cutaneous rash after being immunized with rabies vaccine or meningitis vaccine within 1 week. Meng *et al*[33] analyzed 9.9 million doses of measles-containing vaccines in Anhui province, China from 2009 to 2014, and encountered 478 children having rashes within 72 hours after vaccination (48.3 per million doses). However, the etiology of rash was not mentioned in the above study. In another prospective study from Sichuan province, China, Shu *et al*[34] followed-up 14.3 million vaccination practices, and found 28 children with HSP within 48 hours after vaccination (2 per million). Because there is little information on HSP triggered by immunization, therefore the causal relationship between them is still unclear.

The most unique objective of the present study was to probe the association of triggers with relapse/recurrence. Based on our findings, the mean number of relapse/recurrence was 2.92, and the mean interval was 11.4 weeks; 10.25% of HSP relapsed or reoccurred more than one time within a 3-year observational period. Whether the relapse/recurrence exhibited or not, the infection was the most common predisposing factor of HSP. Prais *et al*[35] reviewed the clinical data of 260 patients with HSP in Israel from 1969 to 2004, and discovered that only 7 cases (2.7%) were hospitalized more than once within 2–3 months of the primary episode, whereas no clinical or laboratory characteristics predicted to HSP recurrence. Beyond our expectations, Calvo-Río *et al*[36] established a multivariable logistic regression model and screened the potential predictors of HSP relapse in 417 Spanish patients; almost one-third patients with HSP experienced at least one relapse and a prodromic infection could significantly decrease the risk of HSP relapse after a 12-year follow-up (OR=0.57, p=0.025). However, it is yet unknown whether these available predisposing factors are involved in HSP relapse/recurrence.

CONCLUSIONS

Although the detailed pathogenesis of HSP is still unclear, several types of predisposing factors have been proved to be the initial step. The multiple environmental factors and genetic backgrounds in China account for different epidemiological features of HSP. However, no published data on the predisposing factors of HSP have been documented

from central China up to now. The present study analyzed, for the first time, the predisposing factors in 1200 patients with HSP from the central China and found that HSP occurred commonly in spring and winter and its morbidity had an obvious west-to-east gradient. The infection was the most frequent predisposing factor of HSP, whereas the clinical manifestations exhibited an obvious heterogenicity according to different predisposing factors. Therefore, the identification of predisposing factors may be beneficial in the prevention of HSP progression and relapse/recurrence.

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Contributors PH conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. YX, JJW and YFW drafted the manuscript. YW, FFL and SS collected data and carried out the initial analyses. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Competing interests None declared.

Patient consent Not required.

Ethics approval Approval for this research was acquired from the Medical Ethic Committee of the First Affiliated Hospital of Anhui Medical University.

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